VA COOPERATIVE STUDY #424

Clinical Outcomes Utilizing Revascularization and

Aggressive DruG Evaluation ***(COURAGE)***

1 Directory of Study Participants

Refer to your site's Operations Manual for current list of Study Participants

2 Patient Selection – Screening and Randomization

2.1 Patient Selection

2.1.1 Referrals

The participating investigators should outline and periodically review the goals of this study with the service chief, staff physicians and house staff in order to encourage and facilitate referrals. An effort should be made to notify other community physicians who may see and treat patients with chronic angina pectoris (Canadian Cardiovascular Society [CCS] Class I-III), stable post-MI patients, and asymptomatic (or "silent") myocardial ischemia who have either single-vessel or multi-vessel CAD about the existence and purpose of the study

2.1.2 Screening

Potential study subjects are patients who have or are about to undergo diagnostic coronary angiography will be screened for possible trial entry. If a patient is eligible, and his or her physician agrees, he or she should be approached about participating in the trial.

The tool to screen patients is the screening log (FORM 1). All of the potential study subjects should be entered into the screening log, identified by the last four digits of their Social Security Number / Social Insurance Number. For those sites that may not be able to access the patient's SSN/SIN, use a sequential four-digit number starting at 0001 on the screening log.

2.1.3 Clinical Evaluation

All potential study subjects should be evaluated clinically. Patients who have any of the exclusion reasons, as per protocol, are ineligible for the study and should not be evaluated further.

2.1.4 Angiographic Evaluation

Patients suitable clinically should be evaluated angiographically. Patients will be ineligible if they have any of the exclusions specified in the protocol. If antecedent diagnostic cardiac catheterization has not been performed, informed written consent should be obtained prior to the coronary angiography especially if the patient will be revascularized during this trip to the catheterization lab (see informed consent). If the diagnostic catheterization has already been performed, it should have been no longer than 90 days prior to study entry, with no intercurrent events.

2.1.5 Data form

The Screening Log (FORM 01) should be used to facilitate the screening of patients. Only record patients who are referred for, or already have had, a diagnostic angiogram.

2.2 Pre-randomization Non-invasive Testing

Patients who are eligible based on the clinical inclusion/exclusion criteria will first undergo noninvasive diagnostic testing:

2.2.1 Documentation of ischemia

*2.2.1.1 **Stress testing***

Stress testing to verify or quantify objective evidence of inducible myocardial ischemia or regional wall motion abnormality will be performed. **The preferred method** (see Section 2.2.3 for details) will be exercise myocardial perfusion scintigraphy -- Tc-99m sestamibi gated SPECT.

In patients who are able to exercise, a standard treadmill exercise without perfusion scintigraphy can be used, provided the baseline ECG-ST segment is not rendered uninterpretable (e.g. digoxin effect, left ventricular hypertrophy, left bundle branch block, pacemaker, etc).

In patients who are unable to exercise (or unable to achieve at least 5 METS of exercise), either pharmacologic stress (adenosine) in conjunction with perfusion scintigraphy (Tc-99m sestamibi) to detect reversible defects, or exercise radionuclide ventriculography or dobutamine 2-D echocardiography to detect ischemia-induced regional wall motion abnormalities can be used.

*2.2.1.2 **ECG***

Resting or ambulatory ECG documentation of ischemia (ST-T wave changes in two or more contiguous leads within a lead group).

2.2.2 Left Ventricular Ejection Fraction Assessment

Assessment of left ventricular ejection fraction by one of the following:

a) cardiac catheterization,

b) gated technetium sestimibi perfusion scan,

c) 2-DE (quantitative), or

d) radionuclide ventriculography.

2.2.3 Preferred Method for Documentation of Ischemia

The preferred modality for noninvasive stress testing is Tc-99m sestamibi gated SPECT. Optimally, this would be performed with a two-day protocol, with both rest and stress studies performed using gated acquisition technique but it is recognized that this may be **impossible in most** pre-randomization situations. Next in line of preference would be to have the stress study performed with gated sestamibi SPECT and the resting study not gated and utilizing Tc-99m sestamibi or thallium-201. The least preferred but acceptable approach would be utilization of a thallium-201 SPECT. For purposes of the data analysis within the COURAGE Trial, if this pre-randomization data utilizes Tc-99m sestamibi and is sent to the nuclear core laboratory, the participating sites will be entitled to partial reimbursement for costs.

The optimal recommended protocol is as follows:

Stress Protocol:	Modified Bruce protocol
Nuclear Protocol:	Day 1: Gated Rest MIBI
	Day 2: Gated Stress MIBI
Isotope:	Technetium-99m-sestamibi

On Day 1, Tc-99m sestamibi is injected, followed by rest Tc-99m sestamibi gated SPECT one hour after injection. For all SPECT acquisitions, adequate tracer dose should be used to allow a minimal acquisition of 300,000–500,000 counts per stop as indicated in the following dose schedule.

Patient Weight (lbs.)	*Dose of Tc-99m Sestamibi (mCi)*
< 185	*25*
185-225	*30*
> 225	*35*

On Day 2, stress testing will be performed by maximal treadmill exercise according to a modified Bruce protocol. In preparation for the stress protocol, beta-blockers should be held for ≥ 48 hours, if clinically feasible. Withdrawal from beta-blockers aids in the assessment of full extent of jeopardized myocardium. When feasible, all other medications should be recorded as to dose and times during the 24 hours prior to testing.

Adequate Tc-99m sestamibi tracer should be injected according the dose schedule above. Heart rate at the time of injection and blood pressure immediately following injection should be recorded. If possible, a two-minute “cool down” period should be performed by continuing exercise at an exercise level at least one stage lower. The acquisition of the post-stress SPECT image should start 15-30 minutes after the end of the stress period.

It is further recommended that all patients be off of caffeine-containing compounds (coffee, tea, decaffeinated coffee, decaffeinated tea, and medications, foods or beverages containing caffeine) for 24 hours prior to exercise stress testing.

If the patient fails to achieve $\geq$ 85% of maximal predicted heart rate during exercise stress testing, the Tc-99m sestamibi should not be injected and the testing should be immediately switched to adenosine stress. The costs of the adenosine and the costs of the Tc-99m sestamibi will be reimbursed to sites upon successful sending of data to the core laboratory.

2.3 Entry Angiogram

2.3.1 Previously performed angiogram

Most patients will have had a diagnostic angiogram before being considered for the study during the screening process. In clinically eligible patients, left ventricular and coronary cineangiograms will be reviewed by the on-site interventionalist to determine suitability for percutaneous revascularization and medical therapy. If the patient's anatomy is suitable, consent for participation in the study should be sought. Once the patient has given consent for randomization the coordinating center can be called for treatment assignment (see 2.5 RANDOMIZATION). This diagnostic catheterization should have been performed no longer than 90 days prior to study entry but should be repeated if there has been an intercurrent event.

2.3.2 Angiogram not previously performed

In some cases the diagnostic cardiac catheterization will not have been performed prior to clinical screening. Some patients will be considered for the study, who are scheduled for an angiogram with the possibility of a PCI, if suitable and randomized to PCI, during the same trip to the Catheterization Laboratory. These patients must be clinically eligible and all noninvasive testing should be completed prior to catheterization. In addition, written informed consent must be obtained prior to the coronary angiography. If the coronary anatomy is judged suitable for catheter-based myocardial revascularization and for medical therapy, the patient is randomized in the Catheterization Laboratory using the envelope system (See 2.5 Randomization).

2.3.3 Protocol for Angiograms.

See Section 7.3.3 for details of the desired standard protocol for image acquisition.

2.3.4 Sealing devices

Vasoseal VHD® and Vasoseal ES® sealing devices are available for use in study patients. Datascope representatives will supply you with some and advise you as to their use.

2.3.5 Data forms

Record the requested information from the angiogram on FORM 2 - Eligibility and Randomization. Complete Form 2A Angiography Worksheet. This form will be shipped with the films and gives critical information to the core laboratory.

2.3.6 Shipping

Send film, Angiography Worksheet, and, if available, a section of catheter to the core laboratory. If the patient is randomized to angioplasty, send the diagnostic film and the angioplasty film together. See Section 7.4 for details.

Note CHD patients with diabetes who undergo cardiac catheterization should receive non-ionic contrast media to minimize the risk of subsequent renal failure.

2.4 Informed Consent

If the patient is suitable for the study both clinically and angiographically, consent to participate in the study should be sought. The participating investigator or his/her designee will explain the contents of the informed consent document (FORM 10-1086) to the eligible subject. The patient is informed of the purpose of the study, the treatment groups, randomization procedure, and the risks and benefits of participation. The patient is also informed that he/she may refuse to participate, and that even if he/she consents to participate it is still possible to withdraw from the study at any time.

The content in the informed consent document (FORM 10-1086) will be read by the patient and further explained by the participating investigator or his/her designee in the presence of a witness. The patient will also be given supplementary material about PCI, coronary stents, and the medications and possible side effects from the medication. The various strategies will be described and the general intent of the study will be described including the risks of all procedures.

When the presentation is completed and it is clear that the patient understands the information, the patient will be asked if he/she wishes to consent to participate in the study. If the patient is willing, he/she must then sign FORM 10-1086 in the presence of a witness. The witness should preferably be the spouse, a family member, a friend of the patient or possibly a hospital staff member (not study personnel), who can witness the patient's signature. The witness will sign and date FORM 10-1086 and give his/her address. The physician, or study person who explained the study to the patient will also sign the form.

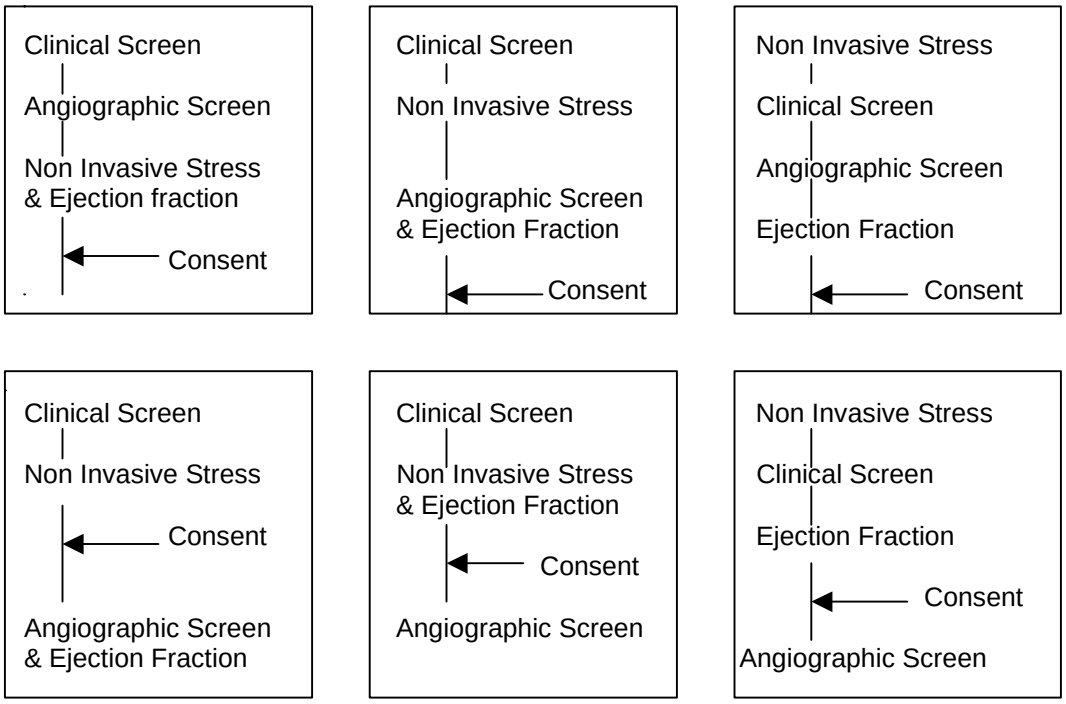
If the patient does not consent to participate, he/she will not be admitted to the study, but will be assured of receiving the best possible care in any case.

The original consent form will be placed in the patient's permanent hospital record.

Patients who are being considered for the study and who are scheduled for an angiogram with the possibility of a PCI if suitable and randomized to PCI should be consented prior to the scheduled catheterization. The study should be explained to them as above, but in addition the possibility that their anatomy may preclude their entry into the study must also be explained to the patient.

Following are a number of schema indicating times during the screening process of a patient when tests might occur and when informed consent could be obtained

2.4.1 Some Schemes for Timing of Evaluations and Informed Consent



2.4.2 Data Form

For a patient that consents to the study and is randomized, the signed consent form should be distributed as described in Section 8.4

For patients who are eligible but do not consent to participate, please complete Form 02 – Eligibility and Randomization. Enter the hospital number but leave the patient number blank. For such patients data collection ends here.

Patients who consent but who are found to be ineligible upon subsequent angiography are not randomized to the study. Enter the relevant data on FORM 1 Screening.

2.5 Randomization

2.5.1 Routine Telephone Procedure

If the patient satisfies all the clinical and angiographic eligibility criteria and has given written informed consent, the patient is ready to be randomized.

1) Call assistant at the Coordinating Center (phone numbers in 2.5.2)

2) Confirm the patient's eligibility.

3) Discuss the patient's stratum

4) The patient is assigned the next sequential number in the appropriate stratum.

5) Assistant will give the clinical coordinator the treatment assignment.

6) The nurse then takes the randomization envelope imprinted with the number, records the patient's name and other requested identifying information on the outside of the envelope and sends it, UNOPENED, along with the other eligibility and baseline information to the Coordinating Center.

2.5.2 Phone Numbers to use for Randomization calls

Research Coordinators:

Toll Free: (888) 803 – 5560

Ray Kilstrom	(203) 932-5711	Ext. 3767
Liz Petrokaitis	(203) 932-5711	Ext. 3760

Alternate Contacts:

Joan Smith	(203) 932-5711	Ext. 3765
Tassos Kyriakides	(203) 932-5711	Ext. 3771
Pamela Hartigan	(203) 932-5711	Ext. 3773
Tenya Marie Economou	(203) 932-5711	Ext. 3762

2.5.3 Procedure for patients in whom the angiogram and the PCI will be done together

If the coronary angiogram is not available but is scheduled with the possibility of immediate PCI if the patient is randomized to PCI plus aggressive medical therapy, the clinical coordinator will call the Coordinating Center (see numbers in 2.5.2) prior to the scheduled catheterization to

1) review the checklist confirming the patient's eligibility,

2) discuss the stratum, and

3) alert the Coordinating Center that a randomization may be imminent.

If the angiogram reveals that the patient's anatomy is suitable for percutaneous revascularization or medical therapy the computer generated envelope system should be used to determine the treatment assignment.

2.5.4 Computer generated envelope system.

A "backup" computer generated envelope system is available for use in the Cath Lab as described in the previous section, and for other emergency situations when it proves impossible to contact the Coordinating Center.

To use the envelope system:

1) Determine the patient's stratum; No Prior CABG or Prior CABG,

2) Select the next sequential envelope in the appropriate group

3) On the OUTSIDE of the envelope record the patient's name and other requested identifying information

4) Open the envelope and proceed to administer the designated treatment

Send the opened envelope along with the other eligibility and baseline information to the Coordinating Center. If the envelope system is used the Coordinating Center must be informed as soon as possible after the randomization, at least by the next working day.

Data Forms

Complete FORM 2 Eligibility and Randomization, after the patient is randomized Complete Form 06 Exercise/Stress and, if appropriate, Form 07 Imaging Evidence of Ischemia. In addition, the randomization envelope and Form 2A angiography worksheet should be filled out.

2.6 Randomization Checklist

Randomization Checklist

1. Meets Clinical Inclusion and Exclusion Criteria _____
2. Presence of Inducible Ischemia _____
3. Angiographic Inclusion Criteria _____
4. Informed Consent Signed _____
5. Coordinating Center Called _____
6. Clinical Case Report Forms
   - A) Form 02 Randomization _____
   - B) Form 06 Exercise/Stress Test _____
   - C) Form 07 Imaging Evidence of Ischemia _____
     (if stress test with nuclear imaging)
7. Form 2A Angiography worksheet completed _____
8. Randomization envelope completed _____
   (opened or unopened)

3 Baseline Evaluations and Procedures

3.1 Baseline - FORM 04

A baseline physical and history should be done, demographic and risk factor information will be collected, recorded on FORM 04. Comorbidities active at the time of randomization are also recorded on this form. The comorbidities specified here are those which are components of a Charlson's comorbidity index.

3.2 Patient Information -FORM 03

Home address and alternate address, either work or summer/winter home, and other contact information should be recorded on FORM 03. This form should be placed in the essential documents binder.

3.3 Laboratory Values - FORM 08

Patients should have fasting blood drawn for local lipid profile and glucose level. Liver enzymes should also be measured. Whole blood for glycated hemoglobin A1c should be drawn for all patients. These values should be recorded on FORM 08.

3.4 ECG

A routine 12 lead resting ECG should be performed. A label should be affixed and the ECG tracing sent to the Coordinating Center along with the baseline forms.

After checking, CSPCC will forward the ECGs to the core ECG laboratory for analysis.

3.5 Quality of Life

Patients should use the Epimetrics application on the pentablet to complete the baseline Quality of Life assessment. This includes:

1. Seattle Angina Questionnaire
2. SF-36 and Mood screen
3. Social support Index
4. Symptom Distress

Patients should also do the utility assessment – Standard Gamble or as it is referred to on the schedule on the pentablet the "Trader." The concepts in the trader may be difficult for the patients to understand at first.

NOTE: If the pentablet is not functioning, paper versions of all forms except the Standard Gamble assessment are available. Remember to use a "master", not a photocopied version. **The coordinating center should be informed as soon as possible about problems with the pentablet.** If the computer is working but the Epimetrics application fails to load call the economic core laboratory at Emory for help- see Section 9 for details.

Data from the completed questionnaires should be saved onto a floppy disk and mailed to the economic core laboratory every 2 weeks. *See Section 9 – Pentablet for further details*.

3.6 Other Patient Completed Forms

The patient should also complete:

a) the Patient Economic Questionnaire (PEQ, FORM 20B),

b) the MEDFICTS diet questionnaire (FORM 15) (note: the pentablet can be used to score the MEDFICTS questionnaire) and the PACE readiness to change eating habits counseling form,

c) the PACE EXERCISE review and readiness to change, and

d) the PACE SMOKING cessation review and readiness to change, if appropriate.

The scores from the MEDFICTS, exercise and smoking reviews should be recorded on FORM 04 – Baseline. The scores should be used to initiate discussions with the patient about appropriate risk factor goals after the patient has completed the readiness questions. *See Section 4.4 Lifestyle modifications for further details and the PACE Manual.*

3.7 Cardiac Medications – FORM 09

Once intensive medical therapy is initiated, (see Section 4.2) the cardiac medications initially prescribed for the patient should be recorded on FORM 9. All cardiac medications have been listed in a code sheet, each class has been given an alphabetic code and each drug within the class has been assigned a number. This should be used to record the information.

3.8 Patient Randomized as an Inpatient

If the patient is hospitalized at the time of randomization, then FORM 11-Hospitalization (and if appropriate FORM 12 – Cardio/Cerebro Vascular Tests) should

be completed after discharge. If it is a US non-VA hospital a copy of the UB92 must be obtained from the finance office.

3.9 Randomized to Angioplasty

If the patient is assigned to PCI and the angioplasty is not being performed along with the diagnostic angiogram, make arrangements for the procedure to be done as soon as possible. The angioplasty should be performed within 105 days of the diagnostic angiogram.

3.10 Next Appointment

At the time of randomization, or before discharge from the hospital, make an appointment to see the patient in approximately 1 month.

3.11 AHA Pamphlets

Several AHA pamphlets will be available for distribution to the patients, as needed.

3.12 Baseline Checklist

BASELINE	
1. Clinical Case Report Forms Completed	
A) Form 04 Baseline	_____
B) Form 03 Patient Information	_____
C) Form 08 Laboratory results	_____
D) Form 09 Cardiovascular Medications	_____
E) Form 10 PCI Procedure (If appropriate)	_____
F) Form 11 Hospitalization (if appropriate)	_____
G) Form 12 Cardio/Cerebro Vascular Tests (if appropriate)	_____
H) Form 19 Report of Death (If appropriate)	_____
I) Form 18 Serious Adverse Event (If appropriate)	_____
2. Quality of Life Data Collected on the Pentablet	
A) Social Support Index	_____
B) Seattle Angina Questionnaire	_____
C) Symptom Distress	_____
D) RAND-36/Mood	_____
E) Standard Gamble- “Trader”	_____
3. Other patient completed forms	
A) Form 14 - PACE exercise and smoking review, Form 15 - MEDFICTS	_____
B) Form 20B - Patient Economic Questionnaire	_____
4. OTHER Procedures/Information	
A) ECG done	_____
B) PACE Counseling initiated	_____
C) Intensive medical therapy begun	_____
D) Discharge summary and documentation collected, as required	_____
E) UB92, if appropriate	_____

4 Post Randomization Management

4.1 Angioplasty

4.1.1 Procedural Guidelines

The operator is free to choose any primary or adjunctive catheter based technique he/she feels would most safely and effectively accomplish myocardial revascularization. The intent is to have the investigator/operator perform as complete a myocardial revascularization as possible while minimizing the risk of procedure-related untoward events. In all patients, revascularization of the "culprit" stenosis, as guided by the previously obtained noninvasive testing, will be undertaken. In patients with multivessel disease, complete revascularization is not mandated if, in the judgment of the operator, this poses undue risk to the patient. Complete revascularization will also not be undertaken, if incomplete revascularization is thought to be adequate, based upon regional left ventricular function, collateral flow to a chronic total occlusion, etc.

Nonsignificant lesions, lesions located distally in small arteries, and lesions that supply areas of infarction will not be dilated.

4.1.2 Planned Strategy

In each patient, the procedural strategy should be predetermined. Most often, revascularization of the lesion that is thought to be most likely responsible for the patient's ischemia should be undertaken first. In some situations, however, initial revascularization of the "nonculprit" lesion may enhance the safety of the subsequent revascularization attempt.

Prior to the procedure the investigator will specify the extent and severity of coronary disease and which lesions are intended for revascularization. Investigators will indicate in advance if the procedure is to be staged. In the event of staging the second procedure should be completed within 2 weeks of the first.

4.1.3 Protocol for the Initial PCI Procedure.

Prior to the procedure, patients will receive aspirin in a dose of 160mg per day for at least 1 day and at least one dose of a calcium channel blocker. The patient will be brought to the catheterization laboratory in a fasting state. Arterial and venous access will be obtained in the usual manner. Heparin will be administered as a bolus of 10,000 units and additional heparin will be given to maintain the activated clotting time above 300 seconds during the procedure.

For angioplasty patients with unstable angina, an intravenous platelet glycoprotein IIb/IIIa receptor inhibitor will be given during the procedure together with unfractionated heparin, with the IIb/IIIa inhibitor continued for a minimum of 12 hours after the procedure.

The periprocedure drug therapy and postprocedure therapy will also be modified in patients undergoing placement of one or more coronary artery stents. At the discretion of the investigator, the access sheaths will be removed 4-24 hours after the procedure, with attention paid to the adoption of a uniform protocol at each site. Following the procedure a calcium channel blocker will be continued for at least 1 month and aspirin (325mg per day) will be continued indefinitely as per protocol. Patients having stent placement are usually treated with ticlopidine in addition for two to four weeks.

4.1.4 Monitoring

Before and within 24 hours after the procedure, a 12-lead electrocardiogram will be obtained and creatine kinase levels with myocardial isoenzymes will be measured at 8 hours and <24 hours or prior to discharge for a total of 2 samples. The ECG will eventually be forwarded to the core lab for analysis.

4.1.5 Films

At the beginning and end of the procedure, a coronary angiogram of the target vessel will be obtained in two orthogonal views with either a **6, 7 or 8 French catheter** after the administration of 200mcg of intracoronary nitroglycerin.

The procedural films for the initial “randomized” PCI procedures will be forwarded to the angiographic core lab for assessment and coding along with the diagnostic film. Although multiple views of each lesion will be evaluated, only end-diastolic frames of the most severe view of the stenosis without fore-shortening will be selected for analysis. See Section 7.3.3 for suggested views.

4.1.6 Sealing Devices

Vasoseal VHD® and Vasoseal ES® sealing devices are available for use in study patients. Datascope representatives will supply you with some and advise you as to their use.

4.1.7 Data forms

Complete FORM 10 for each PCI procedure performed on study patients. For the Initial randomized procedure, also complete the Form 2A Angiography Worksheet and mail with the film (and catheters) to the core laboratory

4.2 Aggressive Medical Therapy

The specific choice of the therapeutic agents for each patient will be left to the discretion of the institutional investigator. Although no specific drugs are mandated simvastatin is the initial drug of choice for lowering LDL cholesterol. The following guidelines are provided to ensure a consistent therapeutic approach with the understanding that a **particular drug may be administered for more than one purpose** (e.g. amlodipine for angina and hypertension or metoprolol for secondary prevention and angina). For specific prescribing information for each drug, indications and contraindications, please see Section 11.

4.2.1 Anti-thrombotic Therapy

Patients should be prescribed aspirin (enteric-coated) 80-325 mg/day. For patients who have an allergy or hypersensitivity to aspirin, clopidogrel should be prescribed in a dose of 75 mg daily.

4.2.2 Anti - Ischemic Therapy

Table 2: Specific Anti-ischemic therapy with or without LV dysfunction

		LVEF > 40%	LVEF <= 40%
Recommend-ations	Secondary prevention (post MI; LV dysfunction)	Q-wave MI: • long acting metoprolol Non-Q wave MI: • diltiazem or long acting metoprolol • + ACE I (lisinopril)	• ACE I inhibitor (lisinopril) • long acting metoprolol (if tolerated)
Guidelines	Symptomatic Ischemia	**Maximize existing drug therapy* • amlodipine • long acting metoprolol (if tolerated) • isosorbide 5-mononitrate	**Maximize existing drug therapy* • amlodipine • isosorbide 5-mononitrate • long acting metoprolol (if tolerated)
	Silent Ischemia only	• amlodipine • long acting metoprolol (if tolerated) • isosorbide 5 - mononitrate	• amlodipine • long acting metoprolol (if tolerated) • isosorbide 5-mononitrate

*maximize drug therapy implies the use of optimal doses within classes

4.2.3 Anti Hypertensive Therapy

All patients whose blood pressure consistently exceeds 130/85 mmHg should be prescribed antihypertensive therapy in keeping with published guidelines (The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure [JNC-VI]; Arch Intern Med 1997; 157:2413-2446). The goal will be to

reach and maintain a targeted blood pressure below 130/85 mmHg. Since myocardial ischemia is necessary to be randomized in this trial, it is expected that many patients will be on beta-blockers (metoprolol) and/or long-acting calcium antagonists (amlodipine). It is likely also that most patients with a prior Q-wave myocardial infarction will be on beta-blockers (metoprolol) and ACE inhibitors (lisinopril), particularly if the left ventricular ejection fraction is below 40%. Many of the patients who have had a prior non-Q-wave myocardial infarction will be on a long-acting heart rate lowering calcium antagonist. If the patient is still hypertensive despite appropriate therapy directed at reducing or preventing myocardial ischemia and medications used for secondary prevention, additional therapeutic choices are suggested. The preferred treatment for patients with diabetes mellitus (types II and I) with proteinuria is an angiotensin-converting enzyme inhibitor (lisinopril). In patients with persistent hypertension despite metoprolol and/or amlodipine an alternative choice is an angiotensin II inhibitor (losartan). If treatment with an ACE inhibitor or angiotensin II inhibitor does not reduce the blood pressure to the target level despite an increase in the doses, JNC VI recommends that a second drug should be added, usually a diuretic. Even in hypertensive patients with diabetes, who have been thought to be adversely affected by diuretics, the SHEP trial has shown that these agents protect these patients against coronary disease to an even greater degree than that observed in their nondiabetic counterparts. The combination of an angiotensin II inhibitor (losartan) and a thiazide diuretic is frequently successful in patients who have persistent hypertension despite anti-ischemic drug therapy.

4.2.3.1 ***Blood Pressure Management***

If the blood pressure remains elevated despite maximum tolerated doses of a given class of agent, the patient may switch to a different class or a second medication from a different class may be added to achieve an appropriate anti-hypertensive effect. Many patients will be treated with metoprolol and/or amlodipine for myocardial ischemia. If the patient is not receiving ACE inhibitors as post-infarction treatment for improving left ventricular systolic function or for treating heart failure one of these agents (lisinopril) or the calcium antagonist amlodipine should be started to control blood pressure with an increase in dose as necessary. ACE inhibitors should also be used for the treatment of hypertension in patients with diabetes who have proteinuria. An alternative drug for the treatment of hypertension would be an angiotensin II inhibitor (losartan) which will be frequently effective in controlling blood pressure in patients who remain hypertensive despite anti-ischemic therapy and use of the appropriate medications for secondary prevention post myocardial infarction. If the ACE inhibitor lisinopril or the angiotensin II inhibitor losartan are ineffective in reaching the target blood pressure, the addition of thiazide diuretic has been recommended by the JNC VI. A combination thiazide diuretic-angiotensin II inhibitor is frequently effective in controlling blood pressure, particularly in elderly patients provided that their EF >39% and they have not had an myocardial infarction within the last 6 months.

*4.2.3.2 **ANTI-HYPERTENSION ALGORITHM FOR COURAGE***

Begin or continue lifestyle modifications

↓

Not at goal blood pressure (<130/85)

↓

Initial drug choice (unless contraindicated) in COURAGE Patients

Anti-ischemic drugs — Metoprolol Or Amlodipine

Compelling indications (based on randomized controlled trials)

- Diabetes mellitus (type 1) with proteinuria: ACE inhibitors (lisinopril)
- Heart Failure: ACE inhibitor(lisinopril), diuretics
- Q-wave MI: B-blockers (non-ISA), ACE inhibitors (with systolic dysfunction)
- Non-Q-wave MI : Heart rate limiting calcium antagonists or beta blockers

Start with a low dose of a long-acting once-daily drug, and titrate dose. Low-dose combinations may be appropriate (e.g. losartan & thiazide diuretic)*.

↓

Not at goal blood pressure

↓	↓
No response or troublesome side effects	**Inadequate response but well tolerated**
↓	↓
Substitute another drug from different class	**Add second agent from different class (diuretic if not already used)**
↓	↓

Not at goal blood pressure

↓

Continue adding agents from another class

***Losartan is not to be used in patients with LV ejection fraction ≤ 39% or within 6 months of AMI

4.2.4 Lipid Altering Therapy

4.2.4.1 Goals:

Primary : **LDL 60-85 mg/dl (1.56-2.21 mmol/L)**

Secondary: **HDL > 35 mg/dl (0.91 mmol/L)**
TG < 200 mg/dl (2.26 mmol/L)

4.2.4.2 Lipid Exclusion Criteria:

Fasting TG > 400 mg/dl (4.52 mmol/L), LDL > 250 mg/dl (6.49 mmol/L) (> 200 mg/dl [5.19 mmol/L] in patients already on a statin at baseline)

4.2.4.3 Lipid Drug Exclusion Criteria:

Fibric Acid Derivatives (gemfibrozil and fenofibrate**)**

*****If, in the opinion of the investigator or study coordinator, it is very likely that a patient who is taking a fibrate and is under evaluation for entry can have the drug withdrawn without a rise in TG > 400 mg/dl (4.52 mmol/L), the subject can be considered for randomization and the fibrate should be discontinued if the subject is randomized.

4.2.4.4 LIPID ALGORITHM FOR COURAGE

BASELINE:

A lipid profile (preferably fasting) should be obtained as part of the evaluation of the patient for participation. Discontinue lipid-lowering medication unless it is simvastatin.

STEP 1: INITIATING STUDY THERAPY

a. For subjects not on any lipid medication at baseline:

LDL (mg/dl)	(mmol/L)	Initial Rx (mg)
<100	2.60	simvastatin 10 qhs
100-129	2.60-3.37	simvastatin 20 qhs
≥130	≥3.38	simvastatin 40 qhs

b. For subjects on statin other than simvastatin at baseline: See equivalency table in Section 11 – Drug and Device Information

LDL (mg/dl)	(mmol/L)	Initial Rx (mg)
If ≤ 85	≤2.21	simvastatin at equivalent dose
If > 85	>2.21	simvastatin dose at one step higher than current equivalent

c. For subjects on simvastatin at baseline: GO TO STEP 2.

STEP 2: TITRATING THERAPY.

a. If LDL is > 85 mg/dl (2.21 mmol/L) at the next visit after starting simvastatin (or at baseline in subjects already on simvastatin):

Double simvastatin dose each 4-6 weeks until LDL ≤ 85 mg/dl (2.21 mmol/L) or dose = 80 mg.

b. If LDL is > 85 mg/dl (2.21 mmol/L) on simvastatin 80 mg, add bile acid binding resin, titrate up per protocol (see table)

c. If LDL ≤ 85 mg/dl (2.21 mmol/L) on simvastatin 80 mg + resin, continue therapy

d. If LDL > 85 mg/dl (2.21 mmol/L) on simvastatin 80 mg + resin at maximum tolerated dose, contact COURAGE lipid consultant

See Section 11 for specific dosing information.

4.2.4.5 SECONDARY GOALS

If LDL < 85 mg/dl (2.21 mmol/L) on simvastatin 10 mg.

AND TG > 200 mg/dl (2.26 mmol/L)

OR HDL < 35 mg/dl (0.91 mmol/L)

ADD Niaspan (see instructions in Section 11 for dosing information)

THE DOSE OF SIMVASTATIN SHOULD GENERALLY NOT EXCEED 10 MG IN PATIENTS TAKING CONCOMITANT NIACIN.

4.3 Diabetes Mellitus

4.3.1 Diagnostic Criteria

1. Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. Fasting plasma glucose (FPG) ≥ 126 mg/dl. Fasting is defined as no caloric intake for at least 8 hours.

or

3. 2hPG ≥ 200 mg/dl during an OGTT. The test should be performed as described by WHO (2), using a glucose load containing the equivalent of 75-gms. anhydrous glucose dissolved in water.

or

4. Patients taking oral hypoglycemic medication or insulin.

4.3.2 Treatment Goals

HbA1c < 7.0%

4.3.3 When to Refer to Primary Care Physician (PCP) for Action

In patients not previously identified as diabetic if FPG > 126 on routine testing refer to PCP for diagnostic workup.

In diabetic patients if HbA1c >7.0% refer to primary care physician.

4.3.4 Goal for Management of Diabetic Patients

The goal for diabetes mellitus management in the COURAGE trial will be to maintain levels of HbA_{IC} <7.0% in diabetic patients. This is the goal for patients who are diabetic at baseline and those who become diabetic during the trial.

4.4 Lifestyle Modification and Counseling

4.4.1 Nutrition and Diet

Goal: <30% of energy intake from fat
<7% from saturated fat
<200mg cholesterol per day

A baseline dietary evaluation will be obtained by the clinical coordinator using MEDFICTS (FORM 15). As an overall goal, study subjects should be instructed by the nurse or a dietitian to achieve and maintain an AHA Step II diet (see end of this section for details/definition of Step I and Step II). Calories restricted as needed to achieve ideal body weight, and fat intake may be liberalized if hypertriglyceridemia results from the low fat/high carbohydrate study diet.

The PACE Nutrition Program provides some practical tools to enable coordinators to quickly, safely, and effectively promote healthful dietary changes for the patients at regular office visits. See Section 4.4.5 and PACE manual for details.

Some AHA pamphlets concerning diet are available for distribution to the patients, if it is deemed appropriate. The MEDFICTS questionnaire is used frequently throughout the study to monitor the patient's adherence to the diet. The results (tables and/or plots) can also be used in counseling the patients and used to review with them their eating habits.

4.4.2 Weight Control

Following the current recommendations, the patient's body mass index (BMI) will be used for the definitions and goals for weight control.

Weight Category definitions	BMI
Desirable	< 25
Overweight	25.0-29.9
Obese	≥ 30.0

Weight Loss Goals	Initial BMI	Goal
	25-27.5	BMI < 25
	>27.5	10% relative weight loss

Calories should be restricted and physical activity increased, as needed, to achieve weight goals.

4.4.3 Physical Activity

Goal: To increase patient's activity level with a goal of 30-45 minutes of moderate intensity activity 5 times a week plus increase in daily lifestyle activities.

At baseline, the subject's current level of physical activity will be assessed using the PACE (Physician Assessment and Counseling for Exercise) questionnaire. Based on the subject's activity level, readiness to change, and treadmill performance, a specific endurance training program will be prescribed by the coordinator. Moderate intensity activities (e.g., walking, jogging, cycling) will be prescribed 5 times/week (minimum: 3 times/week) 30 minutes per session. In addition, an increase in daily activities such as walking breaks at work, using stairs whenever possible, gardening, and doing household work will be recommended. (See section 4.4.7 for some suggestions for patients with limitations)

4.4.4 Smoking

Goal: Cessation

Every subject should be asked at every visit about tobacco use. All smokers will be strongly encouraged to stop smoking. Smokers willing to make a quit attempt will be identified. Smoking cessation clinical practice guidelines from the AHCPR will be used to assist the subject in quitting (JAMA 1996;275:1270-1280). These are incorporated into the PACE counseling procedure. Individual counseling, nicotine replacement, bupropion, and formal cessation programs may be recommended, as appropriate, to current smokers. Each center will use their existing local smoking cessation programs on an as needed basis.

4.4.5 PACE

The PACE questionnaires for Physical Activity Assessment and readiness to change, the MEDFICTS diet questionnaire, the PACE Nutrition Assessment, and the PACE smoking questionnaire, if appropriate, should all be administered. The scores should be entered on the appropriate form (Form 4 at baseline, Form 13 at follow-up).

*4.4.5.1 **Physical Activity***

First have the patient complete the “WHAT IS YOUR PACE SCORE” assessment.. Record this score on the appropriate form (either baseline or follow-up). Use this score to select the most appropriate counseling protocol for the patient. For example, if the patient circles 2 on the CURRENT PHYSICAL ACTIVITY assessment then you would use the “PLANNING THE FIRST STEP” counseling protocol. The script “PLANNING THE FIRST STEP” gives you some guidance as to what to say to the

patient. Assist or collaborate with the patient in completing the planning the first step plan, including roadblocks. At the end of the planning process ask the patient to assess how confident he/she is that the plan can be carried out. If the patient is not very confident – go back and make the goals more modest or eliminate some of them. Work with the patient. Make a copy of the plan for the patient's record and your use at the patient's next visit. Give the plan to the patient for use at home.

The PACE handbook has much more detail and should be consulted for this process

4.4.5.2 ***Diet***

First have the patient complete the PACE Nutrition Assessment. This has a readiness to change component included. Three nutrition topics are addressed. Given the goals for the trial you should concentrate on the dietary fat intake but all topics can be included as goals for change. As in the physical activity portion the patient's response guides you to the most appropriate selection of counseling protocols. For example, if the patient answers #3 for the fat section then use the CHARTING A COURSE FOR CHANGE counseling protocol. The script component guides you as to how to counsel the patient. Look at the nutrition guide with the patient. Help or collaborate with the patient in developing a plan. Again if the patient is not very confident that the plan can be achieved, adjust it making the goals more modest. Make a copy of the plan for the patient's record and your use at the patient's next visit.. Give the plan to the patient for use at home.

The PACE handbook has much more detail and should be consulted for this process

4.4.5.3 ***Smoking***

Have the patient complete the PACE Smoking Score – CURRENT SMOKING STATUS

Enter the score on the study form. If a nonsmoker, just give praise. Apart from this, the PACE score directs you to the most appropriate counseling protocol. For example, a score of 4 would direct you to THINKING ABOUT QUITTING SMOKING. Collaborate with the patient in developing a plan. Copy for the patient's record and your use at the patient's next visit. Give the plan to the patient for use at home.

The PACE handbook has much more detail and should be consulted for this process.

4.4.6 AHA Pamphlets

Several AHA pamphlets will be available for distribution to the patients on an as needed basis.

AHA Pamphlets

An eating plan for healthy Americans
Walking for a healthy heart
Managing your weight
Smoking and heart disease
High blood pressure control, risk, lifestyle

4.4.7 Physical Limitations

Some suggestions for Physical Activity counseling for patients with physical limitations apart from their CAD: claudication, missing digits, missing limbs, COPD.

1. Talk to the rehabilitation department in your hospital. These professionals may have some very good suggestions or references for you to work with.

2. If the patient can swim or walk safely in shallow water, and a pool is available, suggest swimming and/or water aerobics.

3. There may be a post-stroke or post-MI water exercise program in your area. Check. If there is, ask for help for your physically impaired patients.

4. Suggest Yoga. It may not be aerobic but it is stress reducing. You do not have to have the body of a gymnast and you don't need any special equipment beyond a mat of some sort. There may be a class at a local gym, town center, or YWCA.

5. Check out the book: *The New Adapted Physical Education* by Janet Seaman and Karen Depauw (adapted for persons with limitations). It is being distributed by

AAALF/AAHPERD
1900 Association Drive
Reston VA 20191

for a cost of $40 (members) or $47.50 (non-members). Although oriented toward physical education classes this may be a very useful reference – check with your library it might be possible for them to get it for you.

6. Upper body exercises will provide some aerobic effect and can be done while seated or standing.

7. Weight training. Supervised in a gym may be best, but it can be done at home using cans of soup etc as the weights and concentrating on the upper body alone. Start with light weights and a small number of repetitions and work up gradually.

8. Floor exercises such as sit-ups, leg raises, or push-ups may be appropriate for some patients.

NOTE: Unlike walking, which can be done without any demonstration of "how to", some of the suggestions here will need instruction or demonstration of the "correct" way to do them. Form is often important to avoid injury and to get the best effect.

"Tips for Exercising Success" from the AHA web site
http://www.amhrt.org/health/lifestyle/physical_activity/exertips.html
for the most part applies to these patients too.

4.4.8 Step I and Step II Diet definitions

What dietary therapy for high blood cholesterol is recommended?

Recommended Intake as Percent of Total Calories

Nutrient*	Step I Diet	Step II Diet
Total Fat	30% or less	30% or less
Saturated Fatty Acids	8-10%	7% or less
Polyunsaturated Fatty Acids	Up to 10%	Up to 10%
Monounsaturated Fatty Acids	Up to 15%	Up to 15%
Carbohydrate	55% or more	55% or more
Protein	Approximately 15%	Approximately 15%
Cholesterol	Less than 300 mg per day	Less than 200 mg per day
Total Calories	To achieve and maintain desired weight	To achieve and maintain desired weight

* Calories from alcohol not included.

What are recommended amounts of total fat and saturated fat in grams?

Calorie Level	Total Fat (grams)	Step I Diet Saturated Fatty Acid (grams)	Step II Diet Saturated Fatty Acid (grams)
1200	**40 or less**	**11-13**	**less than 9**
1500	**50 or less**	**13-17**	**less than 12**
1800	**60 or less**	**16-20**	**less than 14**
2000	**67 or less**	**18-22**	**less than 16**
2200	**73 or less**	**20-24**	**less than 17**
2500	**83 or less**	**22-28**	**less than 19**
3000	**100 or less**	**27-33**	**less than 23**

What are the differences between the AHA Diet, the Step I and Step II Diets?

The initial dietary recommendations for patients on Step I are similar to those advocated by the AHA for the public. The only difference is that Step I is to be carried out in the medical setting. For those patients who have not reduced their fat and cholesterol intake prior to treatment, Step I is the initial therapy. For those already on the Step I diet, further reductions in saturated fat and cholesterol - the Step II diet - should achieve more cholesterol lowering. Also, those patients whose cholesterol level is in the high risk range (240 mg/dL and higher) or who have had a heart attack, should be encouraged to immediately adopt the Step II diet. These changes in diet should be carried out along with regular physical activity in all patients and weight reduction in the overweight.

5 Follow-up

5.1 Routine follow-up visits

5.1.1 Procedures

During the follow-up visit lipids and lipoproteins, liver enzymes, body weight, and blood pressure will be monitored. The medical therapy (anti-hypertensive, anti-ischemic, antiglycemic, and lipid therapy) should be evaluated and optimized, as needed. Blood should be drawn for core lipid lab measurement of lipid profile including some for storage (not whole blood*). See the lipid core lab section for the specific details.* This blood should be processed and frozen for shipment at a later date.
The patient's risk factor goals and achievements should also be assessed. Other information, such as ECG, stress test, and Quality of Life assessments will be done periodically. *See Schedule of Tests Section 8.2 for details.*

5.1.2 Visit Schedule and Window for visits

The follow-up visit schedule is 1 month, 2 months, 3 months, 6 months, and then every 6 months thereafter. This does not preclude a patient from being seen more often if his/her clinical condition requires it. However, study data will only be collected on these occasions. There is a window for the completion of follow-up visits; ± 14 days for the first 3 visits, ± 30 days for subsequent visits. In the event of inability to complete a scheduled clinic visit due to hospitalization, intercurrent illness, or logistical constraints, the patient or family should be contacted by phone. When necessary, the patient's primary care physician may be contacted to provide some clinical information.

5.1.3 Scheduling System on Pentablet

A scheduling system has been set up on the pentablet to assist study personnel in scheduling patients and reminding the coordinator and the patient of the next visit. It is suggested that once the patient is being seen only every 6 months that patients be

contacted, by phone, about halfway between visits. *See scheduling handbook for details for use of system.*

5.1.4 ALLOW ADEQUATE TIME.

In scheduling patient visits **adequate** time should be allowed for all assessments and counseling to take place. For example, if a full QOL battery is scheduled a minimum of 40 minutes should be allowed for this alone. If the patient is elderly, at least 1hour should be allotted for the QOL completion. At the beginning, the counseling may also take considerable time.

5.1.5 Contact Information

At each visit the current contact information (phone #, address, other contact person) should be verified. If items have changed, complete a new form (Form 3) with the updated information.

5.1.6 Lifestyle modification – risk factor counseling

This should be done at every visit. *See Section 4.4 and the PACE handbook for details.*

5.1.7 Compliance

Provision of optimal medical therapy depends on the subjects' abilities to initiate and maintain recommended lifestyle changes and medication regimens. Consequently, a case management approach will be used to facilitate these efforts. Interventions will be based on self-efficacy theory, which proposes that the belief in ones' ability to perform a behavior is a major determinant of subsequent behavior. Providing feedback about progress in initiating behavior change may help reinforce the behavior.

During the first visit, the recommended lifestyle changes and medication regimen will be discussed and subjects will be asked to consider how confident they are in their ability to initiate the lifestyle changes. For those subjects who are less than 70% confident more individualized instruction may be needed to address problematic situations.

(DeBusk, RF Miller, NH and Superko R. A case management approach for coronary risk factor modification after acute myocardial infarction. Ann Int Med (1994) 120:721-29

Strategies for Promotion of Medication Compliance and Risk Factor Reduction

Behavior	Assessment Strategy and Intervention	Maintenance Strategy	Feedback Mechanism	Compliance Measure
Medication administ-ration	Assess difficulties with side effects or compliance in the past. Begin non-judgmental approach to compliance assessment. Emphasize importance of taking medication and if difficulties arise to notify clinical coordinator	Number to call for medication problems Dose checklist with times and potential cues for accurate administration at home	Provide positive feedback at clinic visit.	Ask patients about their pill taking patterns and times. Try to be non-judgmental Ask the patients using the Morisky assessment
Exercise	Use baseline exercise stress test and results of PACE questionnaires to establish exercise prescription. Goal of 30 mins of 60-80% peak HR 5 times per week For subjects without a stress test advise to walk briskly for 20-30	Encourage patient to keep a log of miles walked or days exercised. Review log at each visit Use the PACE assessment at each visit.	Provide feedback about stress test results and any subsequent stress results. Provide feedback as per PACE	Follow-up exercise test at 1 year and 3 years to demonstrat e progress. Self report on PACE PACE

Strategies for Promotion of Medication Compliance and Risk Factor Reduction				
Behavior	Assessment Strategy and Intervention	Maintenance Strategy	Feedback Mechanism	Compliance Measure
Exercise (continued)	mins daily at moderate intensity that does not elicit cardiac symptoms Provide instruction about need for warm-up exercise to reduce injury. Standardized scripted PACE counseling about the desirability of exercise.	Continue with the standardized scripted counseling		Score
Smoking cessation	Standardized assessment of smoking status. Standardized PACE scripted counseling about the importance of smoking cessation. Coping mechanisms and barriers to quitting	Continue with the scripted PACE counseling Consider nicotine patches and formal programs for persons with decreased confidence of quitting or with heavy withdrawal symptoms	Provide feedback as per PACE	Self report PACE score
Diet , Nutrition, and Lipid Altering	Use MEDFICTS questionnaire to assess eating habits Use the PACE questionnaires to assess patients willingness to change, and provide targets for calories, fat .	Use MEDFICTS questionnaire to assess eating habits Use the PACE questionnaires to assess patients willingness to change, and provide targets for	Provide chart of MEDFICTS results (on the pentablet) Report Lipid levels to patients	MEDFICTS score PACE score LDL, HDL from central lab

Strategies for Promotion of Medication Compliance and Risk Factor Reduction				
Behavior	Assessment Strategy and Intervention	Maintenance Strategy	Feedback Mechanism	Compliance Measure
Diet, nutrition, and lipid altering (cont)	Begin scripted PACE counseling	Continue with scripted PACE counseling		
Weight reduction	Height and weight at baseline. Use BMI table to determine goal. Consider referral to formal weight reduction program if grossly obese	Review progress of weight loss or gain at each visit	Track weight loss on a graph and show subject	Obtain weight at each visit (without shoes)

5.1.8 If patient cannot attend clinic for visit

If the patient cannot travel to the clinic for a visit, try to contact the patient at home and ask the patient the questions on the follow-up form over the phone. Send the patient the quality of life and risk factor forms for completion at home. Include a self addressed envelope for the patient to use to return the completed forms. Make arrangements for the patient to receive his/her drugs. If reasonable, make arrangements for local measurements of lipids and other blood values

5.1.9 Computer Failure

If the computer fails, call the coordinating center and arrangements will be made for a fix, either a software repair or a complete replacement. If it fails on the morning of clinic

so that there is no time for a fix, please use the paper version of the QOL forms and have the patients who are scheduled for QOL assessment complete as much of it as possible.

5.1.10 Next Appointment

Before the patient leaves the clinic, schedule the next clinic visit with the patient.

5.1.11 Data Forms

5.1.11.1 ***Every Visit***.

The follow-up visit (FORM13), lab tests (FORM 8) and Cardiac Medication (FORM 9) should be completed at **every** visit

The MEDFICTS and PACE forms should also be completed. These forms are **not** copied and sent to the coordinating center but originals should be placed in the patient's study folder.

5.1.11.2 ***Periodic Scheduled Assessments***

The schedule alerts you to the other tests (QOL and components, ECG, and/or Stress test, for example) that need to be done at a particular visit and the resulting FORMS that need to be completed.

5.1.11.3 ***Unscheduled Assessments***

As alerted on the follow-up visit form, if any hospitalizations, cardiac procedures, cardiac tests, or adverse events have occurred since the last routine study visit, the appropriate form -- the hospitalization form (11), cardio/cerebro vascular test form (12), and /or the adverse events form (18) should also be completed.

5.1.12 Scheduled Follow-up Visits Checklist

SCHEDULED FOLLOW-UP VISITS

1. Clinical Case Report Forms Completed
   - A) Form 06 Exercise/Stress Test (1 year, 3 years) _____
   - B) Form 07 Imaging Evidence of Ischemia (if stress test with nuclear imaging) _____
   - C) Form 08 Laboratory Values _____
   - D) Form 09 Cardiovascular Medications _____
   - E) Form 13 Follow-up Visit _____
   - F) Form 03 Patient Information (if applicable) _____
   - G) Form 12 Cardio/Cerebrovascular Tests (if required) _____
2. Quality of Life Data Collected on the Pentablet (Check times for each, table 5) _____
3. Form 20F - Patient Economic Questionnaire (Check times, table 5) _____
4. Routine 12 lead resting ECG (3 and 6 months, then annually) affix label, then mail to West Haven _____
5. Adjust anti-anginal, anti-hypertensive and lipid altering medication _____
6. Refer to primary care physician if HbA1c>7.0% _____
7. Form 14 - PACE questionnaires, Form 15 - MEDFICTS completed and Counseling Given for Exercise/Diet/Smoking _____
8. Blood drawn for Local Laboratory Testing (each visit, FORM 08) _____
9. Blood drawn for Lipid Core Lab (1 month visit, 6 months, then annually) frozen, then shipped _____

5.2 Recurrent Anginal Symptoms

5.2.1 Patients randomized to "Medical Therapy Only ":

If a patient develops worsening or persistent angina after randomization, the following management guidelines will be used:

a) for all but CCS Class IV patients, intensify medical therapy (increase doses of anti-ischemic drugs, and/or add additional agents as needed clinically); if the patient subsequently stabilizes to CCS Class I-II, continue medical therapy indefinitely;

b) if symptoms do not stabilize, or worsen to CCS Class III after 6-8 weeks of **maximum** medical therapy, the patient should undergo stress testing preferably a 1 or 2 day protocol with ECG gated sestimibi SPECT imaging (see section 5.3) and if there is a high risk result (EF<35% or 2 or more areas of reversible defects) the patient should undergo re-catheterization and possible revascularization, as indicated clinically.

5.2.2 Patients randomized to "PCI + Medical Therapy":

If patients "destabilize" clinically after randomization, the following guidelines will be recommended:

a) if the patient is in CCS Class I-II, and there is **no** evidence of spontaneous ischemic ECG changes at rest, a repeat stress test (exercise or pharmacologic, preferably with ECG gated technetium sestimibi imaging) will be obtained, and if this is positive (2 or more areas of reversible defects or EF< 35% , the patient should be considered for re-catheterization.

b) If it is <6 months after randomization and patient is in CCS Class III-IV repeat cardiac catheterization and/or PCI should be performed

c) if it is > 6 months and the patient is in CCS Class III-IV **medical therapy should be maximized first** then if still Class III-IV**,** repeat cardiac catheterization and/or PCI should be performed

5.3 Non-Invasive testing for ischemia

5.3.1 Patients with recurrent symptoms.

Patients who develop worsening of chest pain or declines in activities of daily activities with increasing frequency of angina should be treated as outlined in the previous sections depending on their original treatment assignment and the severity of the symptoms. Many of these patients will be candidates for noninvasive stress testing. The recommended noninvasive stress testing protocol is a two-day rest/stress Tc-99m sestamibi gated SPECT protocol as described below:

Stress Protocol:	Modified Bruce protocol
Nuclear Protocol:	Day 1: Gated Rest MIBI
	Day 2: Gated Stress MIBI
Isotope:	Technetium-99m-sestamibi

On Day 1, Tc-99m sestamibi is injected, followed by rest Tc-99m sestamibi gated SPECT one hour after injection. For all SPECT acquisitions, adequate tracer dose should be used to allow a minimal acquisition of 300,000–500,000 counts per stop as indicated in the following dose schedule.

Patient Weight (lbs.)	*Dose of Tc-99m Sestamibi (mCi)*
< 185	*25*
185-225	*30*
> 225	*35*

On Day 2, stress testing will be performed by maximal treadmill exercise according to a modified Bruce protocol. In preparation for the stress protocol, beta-blockers should be held for ≥ 48 hours, if clinically feasible. Withdrawal from beta-blockers aids in the assessment of full extent of jeopardized myocardium. When feasible, all other medications should be recorded as to dose and times during the 24 hours prior to testing.

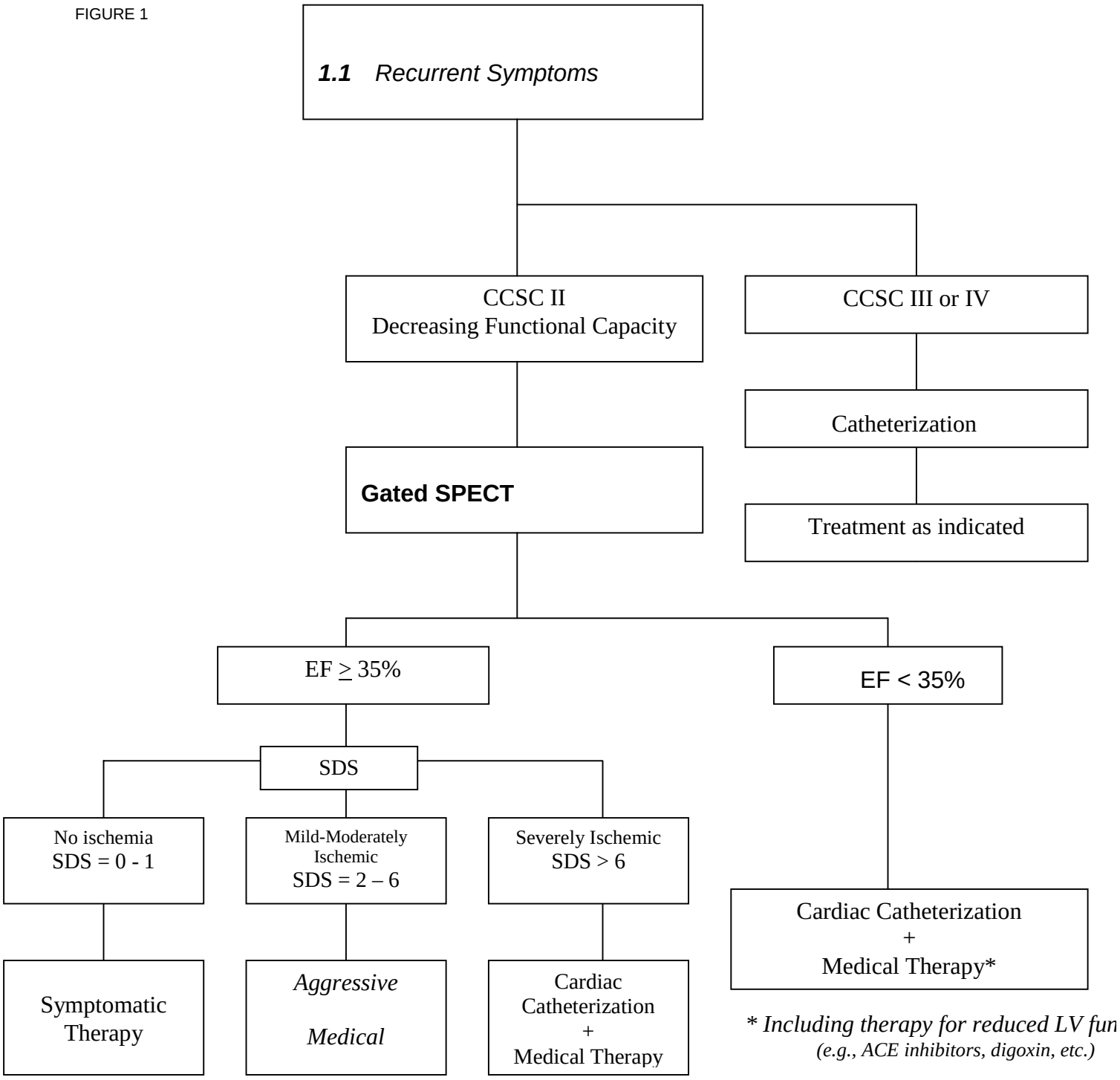
Adequate Tc-99m sestamibi tracer should be injected according the dose schedule above. Heart rate at the time of injection and blood pressure immediately following injection should be recorded. If possible, a two-minute “cool down” period should be performed by continuing exercise at an exercise level at least one stage lower. The acquisition of the post-stress SPECT image should start 15-30 minutes after the end of the stress period.

It is further recommended that all patients be off all caffeine-containing compounds (coffee, tea, decaffeinated coffee, decaffeinated tea, and medications, foods or beverages containing caffeine) for 24 hours prior to exercise stress testing.

If a patient fails to achieve ≥ 85% of maximal predicted heart rate during exercise stress testing, the Tc-99m sestamibi should not be injected and the testing should be immediately switched to adenosine stress. The adenosine and the Tc-99m sestamibi will be provided for these tests.

Patients would then be considered candidates, or not, for repeat catheterization according to the diagram illustrated in Figure 1.

FIGURE 1



1. If patients have EFs < 35% before PTCA, consideration could be given to directly catheterizing them without testing if mild to moderate symptoms recur.

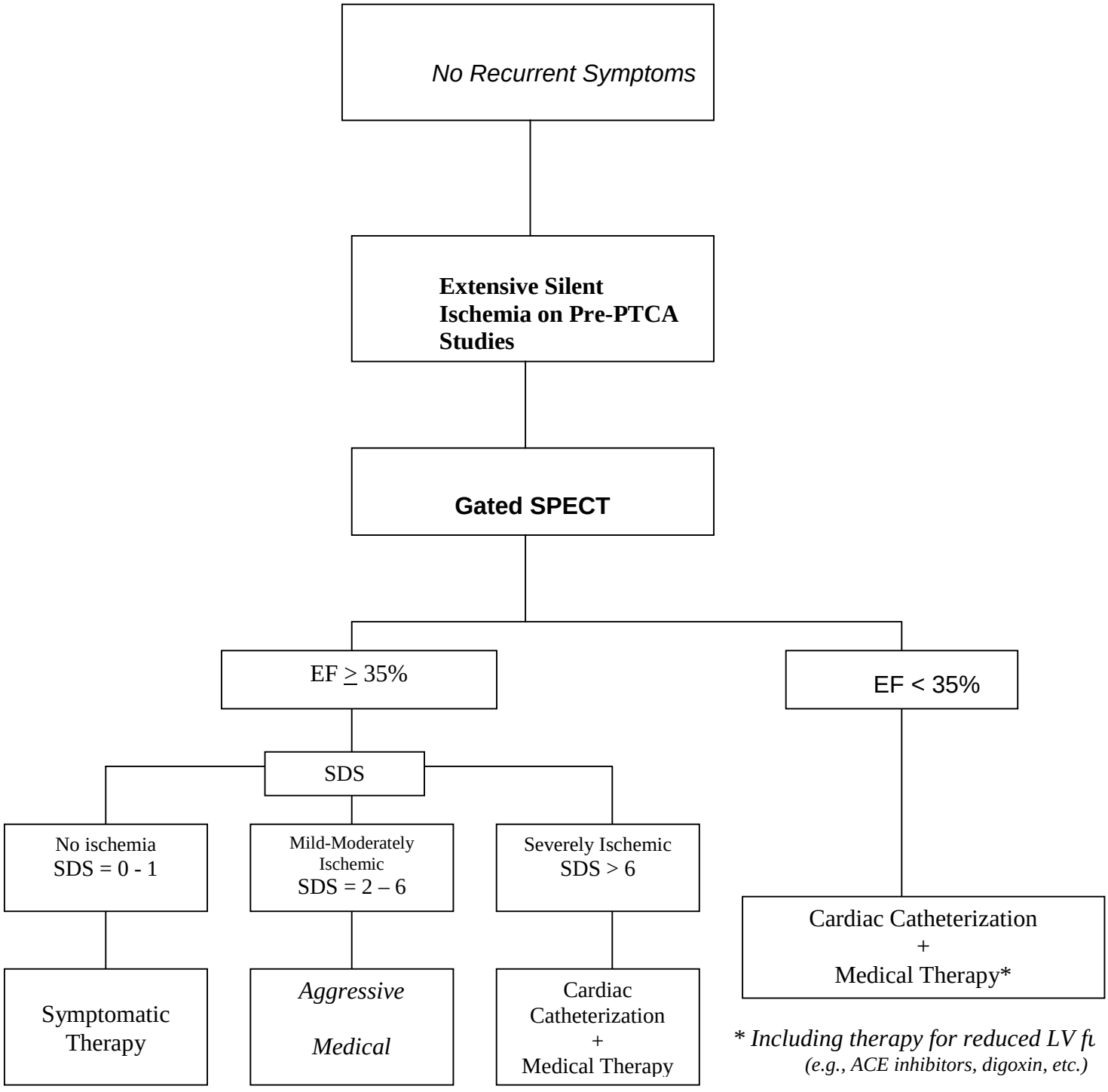
2. The EF noted is the post-stress ejection fraction. An additional consideration for this diagram would be patients in whom the post-stress EF is < 50% and > 5 EF units less than the resting EF. Adding this component would allow the detection of the rare but important patient with diffuse stress-induced ischemia and minimal reversibly perfusion defects.

3. Patients with extensive silent ischemia on their pre-PTCA are illustrated on a separate diagram.

5.3.2 Patients with ischemia and no symptoms at baseline.

Patients in whom extensive silent ischemia (i.e. those in whom there was evidence of extensive ischemia by noninvasive testing in the absence of angina) was the pre-randomization state, noninvasive stress testing may done 3-4 months after randomization. If it is done, the preferred method for such testing is the two-day protocol, rest/stress Tc-99m gated SPECT, as outlined in the previous section. The management of these patients is depicted in Figure 2.

FIGURE 2


No Recurrent Symptoms
Extensive Silent Ischemia on Pre-PTCA Studies
Gated SPECT
EF ≥ 35%
EF < 35%
SDS
No ischemia SDS = 0 - 1
Mild-Moderately Ischemic SDS = 2 – 6
Severely Ischemic SDS > 6
Cardiac Catheterization + Medical Therapy*
Symptomatic Therapy
Aggressive Medical
Cardiac Catheterization + Medical Therapy
* Including therapy for reduced LV fu
(e.g., ACE inhibitors, digoxin, etc.)

5.4 Cardiac Procedures and Tests

5.4.1 Tests.

Each follow-up visit, patients will be queried about tests that have been done on an outpatient basis since the last follow-up visit. If any occurred, record the information on Form 12 using the date of the visit as the date of the form.

If cardiac or cerebrovascular testing, other than left heart catheterizations, is done during a hospitalization this information is also recorded on Form 12 using the date of admission as the date of the form.

5.4.2 Catheterizations

5.4.2.1 ***Who, When***

Cardiac catheterization should be performed in patients with Class IV angina despite an increase in medical therapy or in patients who exhibit a strongly positive non-invasive test (preferably an ECG gated stress Tc-99m sestamibi SPECT scintigram) as indicated by:

a) ECG exercise test showing >2 mm further ST-depression in multiple leads at low level exercise and/or a decrease in blood pressure with exercise

b) Severe exercise (or post stress) left ventricular dysfunction (exercise LVEF ≤35%)

c) Stress-induced large perfusion defect (particularly if anterior)

d) Stress-induced multiple perfusion defects of moderate size

e) Large, fixed perfusion defect with LV dilatation

f) Stress-induced moderate perfusion defect with LV dilatation

g) Echocardiographic wall motion abnormality (involving greater than two segments) developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min)

h) Stress echocardiographic evidence of extensive ischemia

*5.4.2.2 **Data Form***

Record the information for catheterizations on the hospitalization form (Form 11), including use of sealing devices. If there are multiple catheterizations during an admission, details are recorded for only the first one.

5.4.3 PCI

If patients "destabilize" clinically after randomization, the following guidelines will be recommended:

a) if the patient is in CCS Class I-II, and there is **no** evidence of spontaneous ischemic ECG changes at rest, a stress test (exercise or pharmacologic, preferably with ECG gated technetium sestimibi imaging) will be obtained, and if this is positive (2 or more areas of reversible defects or EF <35%), the patient should be considered for re-catheterization and possible angioplasty;

b) if the patient is in CCS Class III-IV after maximizing medical therapy, repeat cardiac catheterization and/or angioplasty should be performed.

*5.4.3.1 **SAQ***

The patient should complete the Seattle Angina Questionnaire prior to the procedure. Use either the paper version or the pentablet, for this PRN use.

*5.4.3.2 **Data Forms***

Record information about the procedure on the hospitalization form, Form 11, and the PCI form, Form 10. A copy of the procedure notes should be included with the hospitalization form. Form 22 - Seattle Angina Questionnaire.

5.4.4 CABG

If the patient has bypass graft surgery, this should be documented on the hospitalization form. Creatinine kinase and MB fraction should be measured within 24 hours of the surgery. Include a copy of the surgical/procedure notes with the hospitalization form.

*5.4.4.1 **SAQ***

If bypass surgery is planned, have the patient complete the Seattle Angina Questionnaire (Form 22, paper version) prior to the procedure.

*5.4.4.2 **Data Form***

Enter the information on the Hospitalization form (Form 11). If the creatinine kinase is >5 x ULN and the MB fraction is >5% provide documentation for a possible MI endpoint.

5.5 Crossovers

5.5.1 Patient assigned to PCI + intensive medical therapy

Patients randomized to receive angioplasty should be scheduled for the procedure as soon as possible. Ideally this would be the same or next day. The longer the time between randomization and the scheduling of the procedure the greater the chance that

the patient will either withdraw from the study or experience an event. These events will be counted in the PTCA randomized group.

5.5.2 Patients assigned to intensive medical therapy alone.

If, during follow-up, a patient develops symptoms that do not stabilize, or worsen to CCS Class III after 6-8 weeks of **maximum** medical therapy, if possible, the patient should undergo stress testing, preferably a 1 or 2 day protocol with ECG gated Tc99m sestimibi SPECT imaging (see Sections 5.2 and 5.3). If there is a high risk result (EF<35% or severe reversible ischemia) the patient should undergo re-catheterization and possible revascularization, as indicated clinically.

If the patient is Class IV despite maximal medical therapy the patient should undergo re-catheterization and possible revascularization, as indicated clinically.

5.6 Intercurrent Hospitalizations

Information about **all** hospitalizations will be collected. At each follow-up visit the patient should be queried about any hospitalizations since the last visit. For all hospitalizations we will collect discharge diagnoses and require a copy of the discharge summary. More detailed information will be collected for cardiac related hospitalizations.

If the patient was admitted to a non-study hospital the name and address of the hospital must be obtained. Have the patient sign a release form for retrieval of the hospital information. If the admission was to a US nonVA hospital charge information via the UB92 will be required as well. The UB92 should be specifically requested on the release form.

5.6.1 Data forms

The hospitalization form should be completed and any associated information as indicated on the form should be provided.

5.6.2 Intercurrent Hospitalization Checklist

INTERCURRENT HOSPITALIZATION

1. Clinical Case Report Forms
   - A) Form 12 Cardio/Cerebrovascular Tests (if appropriate) _____
   - B) Form 11 Hospitalization _____
   - C) Form 10 PCI (if appropriate) _____
   - D) Form 19 Report of Death (If appropriate) _____
   - E) Form 18 Serious Adverse Event (If appropriate) _____
2. Seattle Angina Questionnaire for any Revascularization (angioplasty or CABG) Performed _____
3. Discharge Summary, CK, CK MB, Troponin I, and Chart Material including ECG, if Possible MI or unstable angina Procedure/surgical notes if angioplasty or CABG done. _____
4. UB92 From Finance Office (US non-VA only) _____

5.7 Early Termination from the Study

If the patient withdraws from the study, is lost to follow-up or dies, then complete Form 17 – Non-routine Termination and, if appropriate, Form 19 Report of Death and /or Form 18 Serious Adverse Event. Attach all required documentation.

5.7.1 Early Termination Checklist

EARLY TERMINATION	
1. Clinical Case Report Forms	
A) Form 17 Non-Routine Termination	_____
B) Form 19 Report of Death (If appropriate)	_____
C) Form 18 Serious Adverse Event (If appropriate)	_____

6 Events

6.1 Death

Deaths will be reported on Form 19 Report of Death

The cause of death will be adjudicated to determine whether or not the death is cardiovascular related.

6.1.1 Documentation required

The following documentation is desired

a) the death certificate,

b) if done, the autopsy report,

c) if the death occurred in hospital, the discharge summary.

6.2 Myocardial Infarction.

6.2.1 Definition.

The diagnosis of an MI will be made if

a) there are new Q waves on an ECG at any time during follow-up

or,

b) there is an appropriate clinical history consistent with acute myocardial infarction as well as biochemical confirmation of myocardial necrosis based on total creatine kinase (CK) using one of the following,

i) at least 1.5 times the upper normal limit (ULN) of the hospital laboratory value for spontaneously occurring MI, or

ii) 3 times upper limit of normal in patients undergoing PCI, or

iii) 5 times ULN with MB fraction >5% in patients undergoing CABG.

6.2.2 Documentation required

6.2.2.1 ***Silent MI***

This will be documented on the routinely collected ECG that is sent to CSPCC and forwarded to the core ECG laboratory for analysis.

6.2.2.2 ***Acute MI***

For spontaneously occurring MIs this will be documented on the Hospitalization form (Form 11). A copy of the laboratory slips and the ECG should be submitted along with the discharge summary for the hospitalization.

a) Periprocedural (angioplasty) MIs will be documented by an ECG within 24 hours and cardiac enzymes (total CK) done twice, once at 8 hours and again prior to 24 hours or discharge.

b) MIs post bypass surgery will be documented with cardiac enzymes (total CK and MB fraction) done within 24 hours of completion of surgery.

6.3 Unstable Angina/Acute coronary syndrome

6.3.1 Documentation required

Unstable angina will be documented using the hospitalization form (Form 11). A copy of the laboratory slips and the ECG should be submitted along with the discharge summary for the hospitalization.

6.4 Stroke:

6.4.1 Documentation required

Stroke will be documented on the hospitalization form (Form 11). A copy of the relevant diagnostic testing reports should be submitted along with the discharge summary.

6.5 CHF

Information will be obtained on the Hospitalization form (Form 11) . This includes the New York Heart Association Class.

6.6 Serious Adverse Events

6.6.1 Reasonably attributable to a study drug

If any serious adverse event that it is believed can be reasonably attributed to one of the drugs distributed by the PCC, or to Cardiolite, occurs, the Serious Adverse Event form (Form 18) will be completed within 24 hours of becoming aware of the event. This form should be faxed immediately to the Pharmacy Coordinating Center. A report should be filed even if it is uncertain which of the study drugs is the suspect drug. If the event is fatal or life-threatening the Co-Chairman's office should be notified by phone as soon as it is reasonable.

6.6.2 Procedure related

If a death or life-threatening event occurs that is procedure related notify the Co-Chairman's office by phone as soon as it is possible to do so.

6.7 Adjudication

6.7.1 MI/acute coronary syndrome

All possible acute MIs and hospitalizations for unstable angina will be adjudicated by the endpoints committee. CSPCC will collect together the required documentation and forward a packet to the ECG core laboratory. The information will be analyzed by the core laboratory and the documentation along with a summary of the analysis will be forwarded on to the endpoints committee for adjudication.

6.7.2 Death

Death will also be adjudicated by the committee to assess whether or not the death was a cardiovascular death.

1. Cardiovascular death

Coronary causes
Acute MI
Sudden death within 24 hours of being seen by another person
Unwitnessed death in the absence of other likely non-coronary causes
Death owing to heart failure in the presence of preceding history of CAD
Death related to undergoing a coronary artery procedure.

Non-coronary cardiovascular causes
Cerebro vascular disease, including stroke or other cause

Aortic, mesenteric, renal, or lower limb peripheral vascular disease related to undergoing a non-coronary arterial procedure including, angiography, non-surgical and surgical revascularization
Venous thromboembolic event
Endocarditis/myocarditis
Valvular disease
Other causes to be specified

2. Non-cardiovascular death

Any cancer
Accidental/suicide/homicide/trauma
Other causes to be specified

6.7.3 Stroke

Stroke will also be adjudicated by the endpoints committee.

Do we need definitions or criteria here? Because of tirofiban and clopidogrel is there some increased need to be careful? Do we ask a neurologist to come up with some definiitons?

7 Core Laboratories

7.1 Lipid Core Laboratory

Specimens will be drawn for the lipid lab at baseline, 6 months and then annually. The specimens should be processed as indicated in the Lipid Core Lab Operations Manual. Shipments to the lipid lab should be monthly. Shipping labels will be provided to each site by the Core laboratory.

The following pages contain the details for the blood drawing, temporary storage, and shipping and handling of specimens.

7.2 ECG Core

7.2.1 Analyses

7.2.2 Protocol for acquisition of ECG

Will be provided by the core laboratory

7.2.3 Shipping information

The ECGs should be labeled using the stick-on labels provided by the coordinating center. The patient's study ID and other identifying information, as requested, should be recorded on these labels. The labeled ECG should be sent to the coordinating center with all the other required paperwork and documentation.

7.3 Angiographic Laboratory

7.3.1 Coronary Segments to be Analyzed in COURAGE

The COURAGE Trial will focus the angiographic analyses on 13 coronary segments:

1. left main
2. proximal LAD
3. mid LAD
4. distal LAD
5. first diagonal
6. second diagonal
7. proximal circumflex
8. distal circumflex
9. first or largest obtuse marginal branch
10. intermediate branch (if present)
11. proximal right coronary artery
12. mid right coronary artery
13. distal right coronary artery

These segments are defined and identified by the CASS Site Code. Smaller branches will be excluded. Smaller branches are both, more difficult or impossible to analyze, and are also of less potential clinical relevance.

7.3.2 Quantitative Analyses

Parameters that will be analyzed quantitatively are the maximum, minimum, and mean diameters of the segments as well as the percent diameter stenosis of each segment. Because edge detection even of parallel borders is never perfect or smooth, even the catheter shaft will demonstrate maximum and minimum diameters that could be used to calculate a “percent stenosis” even though one does not exist. In this case, the spurious number is due to the effects of image noise on the “straightness” and

"parallelism" of the detected edges. This situation is obvious and provides no difficulties in the execution of quantitative and angiographic studies. Physiological tapering of the coronary segments, in addition to image noise affecting the coronaries themselves, however, are much more difficult issues to deal with. This is further compounded by the fact that many focal stenoses are worst at branch points, i.e. at the end of a segment where natural tapering is also most evident. Accordingly, although a "percent diameter stenosis" can be derived from almost any segment, subjective qualification and description of such segments is required to ensure that the data is clinically relevant to the usual notion of what constitutes a focal stenosis.

It is important to recognize that the calculation of percent diameter stenosis requires the implicit assumption that atherosclerosis is not present in the normal area. There is, however, no guarantee of this. In fact, increasingly it is apparent that angiographically normal segments in coronary trees showing focal stenoses elsewhere are seldom free of disease. Moreover, there is no consensus on how to designate the "normal" or, more properly, the reference zone. The approach that will be used in this study will be to utilize as the reference zone the most proximal portion of a segment that appears "normal" and to average diameters in this area over the longest length that has relatively constant diameters. This area can be readily determined from the graphic plot of diameter versus segment length. Regions of obvious ectasia will not be used to calculate diameter stenosis. On occasion, the reference zone will be determined from a more distal portion of the segment that appears less involved with atherosclerosis than a more proximal and more narrowed portion. In our experience, the use of interpolated normal diameters causes underestimation of percent diameter stenosis because of

natural tapering and/or lack of a disease free segment in the distal portion of a segment. This method will not be used in this study.

7.3.3 Protocol for Angiograms

If possible, coronary angiograms should be obtained using a standardized protocol .

3. To achieve maximal vasodilation for cine analysis, 0.1 – 0.3 mg of intracoronary nitroglycerin or an equivalent dosage of IV NTG should be given. This must be documented on the Angiographic Worksheet that will be provided. Doses should be repeated if the imaging of a major coronary artery takes more than 20 minutes. If it is not feasible to give intracoronary or intravenous nitroglycerin then 0.4mg of sublingual nitroglycerin, repeated every 20 minutes will be acceptable. If no nitroglycerin is given, a specific contraindication must be documented on the form (allergy, intolerance, hypotension).
4. Overlap of coronary segments with other vessels, catheters or electrodes should be avoided; foreshortening of the segments of interest should be avoided as well. This will require the acquisition of multiple views because the coronary analysis will essentially involve the entire coronary tree. Particular attention will need to be paid to those segments with focal stenosis.
5. Images should be acquired during held inspiration and with little or no panning.
6. Ionic and non-ionic contrast media are acceptable.
7. The optimal views for any given patient cannot be determined until the time of the actual study.

8. Sufficient contrast must be injected to avoid streaming within the coronary that will cause increased variability of analysis. Excessive streaming will result in inability to analyze the film.
9. Image calibration is a critical step in ensuring accuracy of results. Currently, there exists a tremendous number of catheter sizes and types which all have unique imaging (hence, calibrating) characteristics by virtue of their constituents and the relative lumen sizes (e.g. “hi-flow” versus standard catheters). Moreover, it has been demonstrated that 5F catheters are too small to function as adequate calibrating objects and nylon catheters have poor imaging characteristics. **These must not be used**. Accordingly, the best way to ensure that the critical calibration process is adequate is to **use non-nylon, 6F or larger** catheters, document the size and brand used on the provided form, ensure that a portion of the straight and non-tapering part of the catheter is recorded on the cine run and is close to the mid portion of the image (to avoid major effects due to pin-cushion distortion). A segment of the straight portion of the catheter must be sent to the core laboratory with the film for measurement by caliper. If the catheter is changed during the procedure, the second catheter must also be sent and labeled #2. These catheter segments should be properly cleaned (hydrogen peroxide or equivalent agent) and placed in an envelope within the film container.
10. Images should be acquired using magnification mode. The image intensifier size should be recorded on the form.
11. Left ventriculography should be performed in the 30 degree RAO projection.

*7.3.3.1 **Minimum number and types of projections***

The following are suggested as the **minimum number and the types of projections** that should ensure acceptability for final analysis:

Left coronary:	LAO 10-30 LAO 80-90 LAO 45-60, Cranial 20-30 RAO 10-30 RAO 10, Caudal 20 RAO 10, Cranial 20 LAO 45-60, Caudal 20
Right Coronary:	LAO 45-60 RAO 30-45 LAO 45-50, Cranial 20

7.3.4 Shipping Information

a) The baseline catheterization film, the randomized angioplasty film (if appropriate) , the portion of the catheter(s) and the completed paperwork (angiography worksheet for each film) should be sent by Federal Express to:

G.B. John Mancini, M.D.
c/o Eunice Yeoh
Jack Bell Research Centre
Cardiac Imaging Research Laboratory
Room 236
2660 Oak Street
Vancouver, B.C. CANADA
V6H 3Z6

Phone: 604-875-5477
Fax: 604-875-5471

SITES OUTSIDE OF CANADA: IT WILL BE IMPORTANT TO LABEL THE PACKAGES AS FOLLOWS TO AVOID DELAYS IN CANADA CUSTOMS AT THE BORDER. FAILURE TO LABEL THE FILMS AS FOLLOWS MAY RESULT IN SIGNIFICANT DELAYS:

PATIENT X-RAYS FOR RESEARCH PURPOSES, NO COMMERCIAL VALUE

b) Every effort will be made to return the films as expeditiously as possible. Please ensure that the Core Angiography Laboratory has up-to-date information on the individual at the study site responsible for the films, correct mailing addresses and current phone/fax numbers.

c) Videotapes or cut-films will **not** be accepted. CD recordings can be accommodated.

7.4 Nuclear

7.4.1 Substudy

Routine clinical testing for patients with known coronary disease often includes the referral to a stress nuclear or echocardiographic testing for the evaluation of provocative ischemia. In this setting, noninvasive cardiac testing is used to define subsequent therapeutic strategies of care as well as to provide insight into the patient's short- and long-term risk of cardiac events. Cardiac imaging can potentially identify those patients who are at risk for major cardiovascular events and who may benefit in the form of risk reduction by referral to intervention. Unless cardiac catheterization is clearly indicated in a patient with worsening clinical symptoms, routine clinical management would be expected to include the use of stress testing for the assessment of provocative ischemia for disease progression (ACC/AHA Guidelines for Exercise Testing 1997).

Patients may undergo testing prior to study entry, at the time of the study, or for serial evaluation of the patient's ischemic burden. At study entry, physicians may evaluate the functional significance of a given stenosis. For serial testing, physicians may choose to perform routine testing for the reduction in ischemic burden as

determined by the nuclear scan and this information could also be collected in this substudy.

As such, the clinical questions that may be answered within the COURAGE trial will include the predictive value of perfusion abnormalities in identifying clinically significant coronary disease catheterization abnormalities, in therapeutic decision making, and the added value, if any, of nuclear information above and beyond historical and anatomic information.

A second substudy is proposed to examine the short-term effects (i.e., 60-90 days) of medical and surgical therapy on the patient's ischemic burden (as determined on myocardial perfusion imaging). In this study, we will propose enrollment of 300 patients (i.e., 150 patients per study arm) to undergo pre-treatment and treatment stress myocardial perfusion imaging. As it is expected that functional status will improve for patients undergoing initial treatment, patients may exhibit the same amount of provocative ischemia only at higher metabolic workloads. The radioisotope must be injected at the vasodilatation with a pharmacologic stressor (i.e., I.V. adenosine). This substudy analysis would focus on the net reduction in ischemic burden with initial treatment and to correlate nuclear perfusion changes with those observed from quality of life (i.e., functional status and angina thresholds during testing or activities of daily living).

Questions that will be addressed within this substudy include: What is the value of stress-induced ischemia in the identification of post-PTCA restenosis or progression of disease for patients with known coronary disease who present with worsening clinical

symptoms? Can stress-induced ischemia be used to identify patients who may benefit from more aggressive medical intervention?

7.4.2 Protocol for 300 patient substudy

What is it?
Patient selection?
How are patient selected for this substudy?
Are there any specific entry criteria beyond the main study – any exclusions needed

When is the on-treatment stress test to be done. 3 months? 6 months? Symptoms not needed?

The outcome measures are ?

We need a separate informed consent.

7.4.3 Analyses

The Core Laboratory will provide independent review and image analysis. The analysis site will provide independent correlation of the image analysis for answering the principal clinical question on how nuclear imaging may be used to guide clinical decision making in patients with known coronary disease. As such, it is expected that a combination of quantitative and visual, expert overread may be part of the Nuclear Core Laboratories image analysis. Limitations to the use of quantitative measures are that the results may be discordant and not easily assimilated into daily clinical practice. The protocol should include provisions for expert overread of quantitative measures and the use of a 17 or 20 segment visual scoring system.

7.4.4 Imaging Protocol

The nuclear core laboratory will be responsible for developing the testing and imaging protocols used to assure uniform image acquisition and quality control. The Core

Laboratory would provide a semi-quantitative analysis using standardized segmental scoring of the extent and severity of the perfusion abnormality.

7.4.5 Shipping Information

SITES IN CANADA: IT WILL BE IMPORTANT TO LABEL THE PACKAGES AS FOLLOWS TO AVOID DELAYS AT CUSTOMS AT THE BORDER. FAILURE TO LABEL THE IMAGES AS FOLLOWS MAY RESULT IN SIGNIFICANT DELAYS:

PATIENT X-RAYS FOR RESEARCH PURPOSES, NO COMMERCIAL VALUE

8 Forms

Please refer to your site's Operation Manual for instructions on Data Form Completion

9 Pentablet

COURAGE Trial

Pentablet User's Guide

Emory Center for Outcomes Research

Emory University School of Medicine
1639 Pierce Drive, WMB 319
Atlanta, GA 30322

Table of Contents

9.1 Introduction

The Pentablet is a portable computer designed to ease collection of clinical research data. The research coordinator is able to teach patients to enter their answers for the research questionnaires directly into the Pentablet.

For the COURAGE trial these questionnaires include: Seattle Angina Questionnaire (SAQ), Washington U-Trader, Mood Screen, Rand-36 Health Survey, Symptoms Scale, Self-Management Scale, and the Social Support Index.

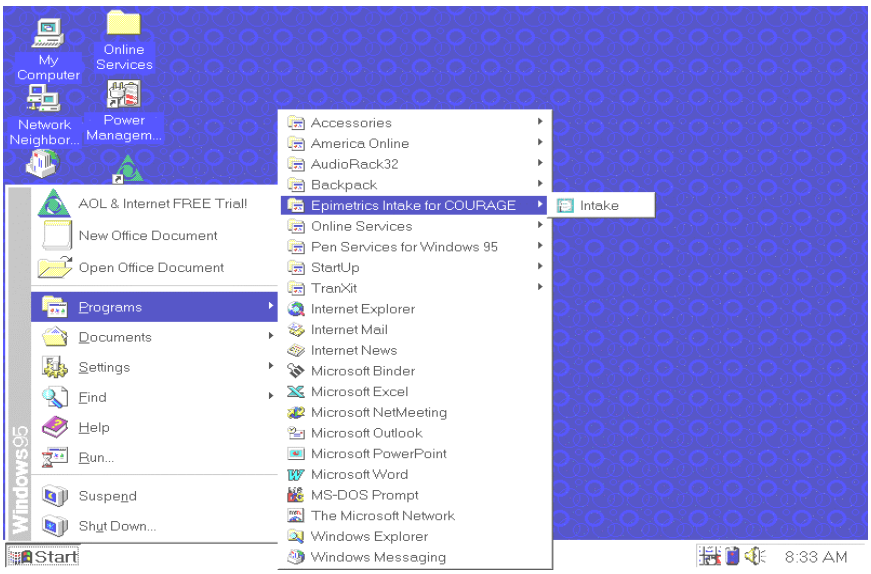
9.2 Instructions for Use

A. Startup

Power up the Pentablet by pressing the power button located at the top left of the Pentablet.
This will start the program and display the initial screen.

If a password is requested, login using "courage".

Using the stylus, tap the START button at the bottom left corner of the screen. Tap PROGRAM, tap EPIMETRICS INTAKE for COURAGE, and then tap INTAKE.



The Epimetrics logo will then appear on the screen. The program is loading and will take approximately 3 minutes to complete.

If the program does not load properly, restart the Pentablet by turning it off and powering up again. If you are still unable to load the program, call Emory Center for Outcomes Research (ECOR) at 404-727-3683.

B. *Patient Enrollment*

Follow instructions for startup. If the screensaver "Welcome to COURAGE" appears on the screen, tap the screen with the stylus to return to a menu screen.

1. The following page will appear. Tap PATIENT ENROLLMENT and then tap NEW. Use this screen to enter a new patient into the system. You may enter just one or several patients at a time. Remember that you enter this information for each patient only once.

2. Attach the keyboard to the keyboard port on the bottom right side of the Pentablet.

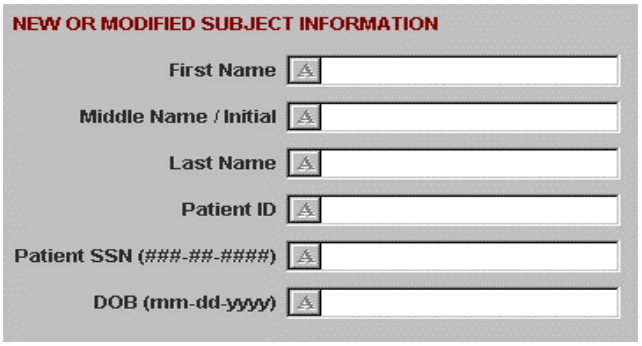
3. Use the keyboard to enter the patient information. Do not enter patient names. Please use only the first initials of the patient's first, middle, and last names. (Lower or uppercase is acceptable).

4. Tap the TAB key or use the stylus to tap after each entry to advance to the next category.

5. Under Patient ID, enter the first three letters of the last name, the first letter of the first name, and the last two digits of the patient's year of birth. (e.g. Joe Smith, 01-01-1940, the Patient ID would be SMIJ40).

6. Enter 123-45-6789 for the patient's social security number (SSN). Please do not enter the patient's real SSN.

7. Tab to the DOB field. This field must be entered using the two-digit month, two-digit day, and four-digit year of birth. Use the format mm-dd-yyyy, e.g. 01-01-1940. If this field is not entered in this specified format, an error message will display. Correct the format and then tap the SAVE button.



If you make an error while entering the patient information in steps 3-7 and have proceeded to a different field you cannot use the backspace (BS) button for correction. You have to use the TAB button or stylus to return to the field containing the error. Once there, the necessary corrections can be made.

8. Once saved, the patient information should appear on the ENROLLED PATIENT list on the right side of the screen. It may be necessary to scroll down the list to ensure this has been accomplished. The newly enrolled patient's information will not appear on the SESSION SETUP list until the program is closed and restarted. To close the program, tap "X" in the upper right hand corner of the screen and restart as previously outlined (see Startup).

9. After restarting the program, the new patient will be listed under SESSION SETUP on the left side of the screen. (Again, this process of loading the program will take approximately 3 minutes).

In order to save battery time, tap START and then tap SUSPEND. This becomes important when you are entering multiple patients' information prior to having them complete their questionnaires.

C. Data Collection

1. Take the Pentablet out of the cradle**.** Place the Pentablet, power cord, keyboard, and folding stand into the carrying case and proceed to the patient location.

2. Hospitalized patients should be approached at a time when they will be able to complete the entire battery of questionnaires. This will take approximately 45 minutes. Currently, once the questionnaires have been started, the partially entered information will be lost if the program needs to be interrupted. It will then be necessary for the patient to redo the entire group of questionnaires.

3. Press the power button and proceed as outlined in STARTUP.

4. Using the stylus, tap SESSION SETUP. Tap on the initials of the patient to be interviewed which should now appear on the left side of the screen under the heading SELECT PATIENT. As previously stated, it may be necessary to scroll down the list to arrive at the correct patient information.

5. Check that the correct date is highlighted on the calendar.

6. On the right side of the screen under SELECT INSTRUMENTS, select the instruments (or questionnaires) to be administered. This can be “All Questionnaires” or “Specific Questionnaires”.

7. Under “Specific Questionnaires”, the appropriate surveys should be selected. It should be noted that the Seattle Angina Questionnaire (SAQ), the Rand-36 Health Survey, and the Washington U-Trader all select as a group and cannot be individually selected. However, all other questionnaires may be selected as single instruments.

8. If a selection error is made, simply tap the questionnaire a second time to de-select the instrument and proceed.

9. Tap BEGIN SESSION. A session will not begin unless a patient’s name has been highlighted in the SELECT PATIENT column.

Care should be taken that the Pentablet is well seated in the folding stand and secured where it is not likely to be tipped over or dropped. It may also help to dim the lights in the room to allow for better contrast in viewing the screen during actual operation by the patient. There are also contrast buttons at the bottom of the Pentablet screen that may be used for this purpose.

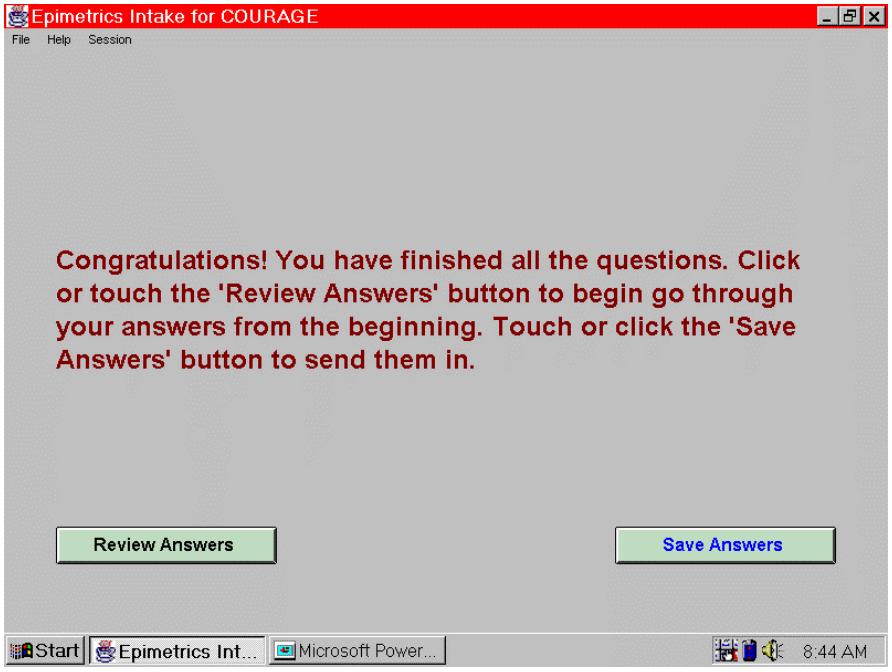
10. Instruct the patient on the use of the stylus. Some patients may find it more comfortable to use the stylus like a pointer as opposed to a pen. The patient should read the question at the top left of the screen and tap on the answer that is closest to their response. Assist the patient in the use of the Pentablet until you are comfortable he/she understands the process.

The Pentablet may be held in the lap. However, due to its weight and the length of time needed to complete the various questionnaires, the recommended method is to place the Pentablet on the folding stand and position it on the bedside table or countertop to allow the greatest ease of operation.

11. Once an answer is selected, the lettering on the answer changes to red. Proceed by tapping NEXT QUESTION and repeat this process until all questions have been answered.

12. If a question is missed, the answer block has been tapped twice, or the answer block has not been tapped firmly enough, a visual prompt will appear. When the CONTINUE box is tapped, the missed question will appear again for the patient to answer. Then the survey questions will continue.

13. At the end of each questionnaire, the screen will display "Congratulations …" and ask the patient to touch or click either the SAVE ANSWERS box or the REVIEW ANSWERS box. Since the patient is prompted throughout each questionnaire to review any missed questions, in the interest of time, instruct the patient to only tap the SAVE ANSWERS box. The Pentablet will loop back into the previous questionnaire if the REVIEW ANSWERS box is tapped until the SAVE ANSWERS box is tapped.



14. When all questionnaires have been completed the screen will read "This session is now complete. Please notify the coordinator." If a patient manages to 'loop back' and restart the program, all the previous information will be lost and the entire battery of questionnaires must be re-answered!

15. Retrieve the Pentablet after the patient completes the questionnaires. The COURAGE Trial screen will again be visible.

16. Tap “X” in the upper right hand corner of the screen to close the program.

17. Tap START and tap SUSPEND. Repeat all steps under **Data Collection** for any subsequent patients each day.

9.3 Data Management

1. Make certain the Pentablet is placed securely in the cradle. Tap on DATA MANAGEMENT. Place a blank 3 ½” floppy disk into the floppy drive bay. The screen will read TRANSFER DATA. Tap LOG TO FLOPPY. A copy of the data will be transferred to the floppy disk. When the green light on the floppy drive goes out or the screen reads “Nothing to Log,” the floppy can safely be removed.

2. Please label the floppy with the site number and the patients logged for that day. A copy of the floppy should be made and kept at each site.

3. Floppy disks should be stored in a dry place away from magnets or other high-energy equipment.

4. Tap the “X” button at the top right corner of the screen. Tap START, then SHUTDOWN. Turn the Pentablet off by pressing the on/off button at the left outside corner of the Pentablet.

5. The Pentablet should be recharged overnight after each day’s data collection has been completed.

10 Good Clinical Practices

10.1 COOPERATIVE STUDIES PROGRAM POLICY

This trial will be conducted in compliance with the Good Clinical Practices (GCP). The term GCP refers collectively to those regulations and guidelines governing the conduct of clinical research. The intent of these regulations is to safeguard subjects' welfare and assure the validity of data resulting from the clinical research.

VA Cooperative Studies Program will assist investigators in complying with GCP requirements through its Site Monitoring Auditing and Resource Team (SMART) based in Albuquerque, NM. This team will present GCP information to the investigators at the study commencement meeting and at later meetings as requested. Also, as described below, SMART will provide manuals and materials to assist clinics in organizing essential study documents and records. Additionally, SMART will be available throughout the trial to advise and assist investigators regarding GCP matters.

While GCP regulations refer to sponsors, investigators and IRBs, the following material focuses on the responsibilities of investigators.

10.2 CSP SOURCE OF GCP MATERIALS AND GUIDANCE

Site Monitoring and Auditing Resource Team (SMART)
VA Cooperative Studies Program
Clinical Research Pharmacy Coordinating Center
2401 Centre Avenue SE
Albuquerque, NM 87106-4180
Telephone: (505) 248-3200
FAX: (505) 248-3206

10.3 INVESTIGATOR STUDY FILES (CONTENT AND ORGANIZATION)

It is essential that the investigator's study records be complete and well organized. Investigator Study File is the term applied by CSP to all records and materials at the participating study clinic pertaining to the study. This includes regulatory documents, correspondence and patient files (both case report forms and supporting medical case records). These documents comprise the Investigator's portion of what FDA terms "Essential Documents" for the conduct of a clinical trial. When combined with the sponsor's portion, they permit evaluation of the conduct of the trial and the quality of the data produced.

For the purpose of organizing the clinic study files, CSP adopts the terminology of the FDA and the International Conference on Harmonization (ICH) Guidelines and recommends categorizing study records as follows.

Essential Documents

I. Sponsor study file (central files)
II. Investigator study file
    A. Protocol
    B. Supplemental Protocol Instructions (Operations Manual, etc.)
    C. Case Report Forms
    D. Investigator Brochure
    E. Consent Form/Patient Information
    F. Subject Log
    G. Serious Adverse Events/Safety Reports
    H. IRB Correspondence
    I. Site-Sponsor Correspondence
    J. Other Correspondence
    K. Telephone/Communications Log
    L. Signature Log/Staff Responsibility & Training
    M. Investigational Product Accountability
    N. Regulatory Documents
    O. Individual Patient Records and Source Documents

Instructional materials provided by CSP to aid in organizing clinic files are as follows:

10.3.1 Essential Documents Binder

SMART will provide specially prepared binders to each participating site to organize and file the regulatory documents, study correspondence and other essential documents using a format recommended for all CSP trials. Variation is permitted; materials can be filed elsewhere with a note of explanation placed in the binder, but it is intended that this binder serve as a directory to all study records and documents contained in the binder and elsewhere. Responsibility for maintaining the binder should be assigned to a specific individual. It is recommended that the binder be readily accessible to clinic staff in the daily performance of their duties.

10.3.2 Subject Case Histories:

FDA requires that investigators keep adequate and accurate case histories for each subject. In this trial, the case history consists of 1) case report forms provided by the CSPCC and 2) the supporting source documents in the patient's medical record.

10.3.2.1 ***CRF Casebooks*** –

It is recommended that a three-ring binder or similar file be assembled for each patient to hold the case report forms arranged by visit. Upon completion of the trial the binder can either be kept intact or be condensed as appropriate.

*10.3.2.2 **Patient Medical Record***

It is recommended that each subject in the trial have a clinic chart (sometimes referred to as a “shadow chart”) to file documents related to the medical treatment and history of the patient during the course of the trial. This clinic chart should be sufficiently detailed to serve as a complete record of the patient’s study participation apart from any official VA Medical Record that may exist for the patient. Where a VA medical record also exists (as it will for veterans), study personnel must make entries to that record as required by VA and institutional policy, e.g., the originally signed consent form must be added to the VA Medical Record.

As a minimum, visit dates and clinician’s comments should be recorded in the clinic chart and/or VA medical record. A progress note should be made for each scheduled visit, even those not attended by the patient. Included in the progress notes should be information on adverse events, concomitant medications, patient compliance with instructions, telephone contacts, and any CRF data not recorded elsewhere in the medical record. It is recommended that the clinic chart also contain hard copies of laboratory reports and all other source documents from which data on the CRFs have been derived, even though these items may be available in the patient’s electronic chart or as hard copy elsewhere in the medical facility.

10.4 IRB-INVESTIGATOR INTERACTIONS

The Institutional Review Board (IRB) is the FDA term for the committee responsible for review of clinical research and protection of patient rights and welfare at the institution. In the context of GCP regulations, this committee is critical to the

research process and operates independently of the investigator and sponsor. In CSP trials, a central IRB called the Human Rights Committee (HRC) reviews the protocol and consent form during the planning process. During the trial, the central IRB is joined by the IRBs of the participating institutions in performing an on-going review of the trial. The IRBs at VA Medical Centers consist of the Research and Development (R&D) Committee and its Human Studies Subcommittee, often a committee from outside the VA Medical Center.

CSP must rely on each investigator to assure the IRB operates in compliance with GCP regulations and that the trial is appropriately reviewed. Prior to initiating the trial, the investigator presents the protocol and consent form to the R&D Committee for IRB review and revises the prototype consent form provided in the protocol as necessary to meet institutional requirements. The investigator must resubmit the trial for review annually or more often if required by the IRB. Additionally, the investigator must report to the IRB all unexpected risks to patients (e.g., serious adverse events), proposed recruitment advertising and proposed protocol changes. Deviations from the protocol, whether approved or unapproved, do not constitute protocol changes, but would be reported to the IRB if associated with unanticipated risk.

Whenever possible, CSP will notify investigators of items requiring IRB review, but it is the investigator's responsibility to determine what items need be reported to or approved by their local IRB.

10.5 PATIENT INFORMED CONSENT

Protection of the rights and welfare of patients is a primary concern of the VA Cooperative Studies Program. Informed consent will be documented in this trial by the use of a consent form prepared by each investigator and approved by the investigator's IRB. The prototype consent form provided in the protocol may be adapted to meet local needs. This form has been reviewed by the central IRB at the CSPCC and contains the basic required elements of informed consent. The consent form, as revised and approved by the local IRB, must be sent to the CSPCC before the trial may begin.

Obtaining Informed Consent - Getting the patient to sign the consent form does not constitute informed consent, but use of the form aids in assuring subjects are receiving adequate and consistent information about the trial and have consented to participate. In this trial, the investigator or qualified sub-investigator must meet with the patient to afford opportunity for questions before the patient signs the consent form. The investigator will sign and date the form on the day the meeting with the patient occurred.

The patient will be given a copy of the form. A progress note is required to document that the patient consented prior to study participation, i.e., any procedure associated with risk or discomfort performed for study purposes rather than for patient care.

10.6 INSPECTIONS OF INVESTIGATOR SITES

10.6.1 By CSP

Routine site visits by clinical trials monitors are not planned for this trial. Each site, however, may expect to be visited at least once during the trial by a GCP auditor from the team in Albuquerque. The investigator will be contacted prior to the visit to arrange a mutually agreeable time for the visit. The auditor will be at the site for approximately two days reviewing study records and discussing conduct of the trial. Following the visit, a Certificate of Audit will be sent to the investigator with a summary of findings and observations. The certificate is to be filed in the Essential Documents binder. A copy of the Certificate is sent the VA CSP Headquarters. CSPCC may conduct human rights site visits at selected clinic sites in conjunction with its Human Rights Committee.

10.6.2 By FDA

While visits by FDA inspectors are unlikely to occur while the trial is on-going, a visit may be scheduled at any time. The investigator will be notified of an impending FDA inspection either by the Cooperative Studies Program or by direct contact from the FDA inspector. If notification is received directly, the investigator should contact the CSPCC and SMART in Albuquerque. SMART will send one or more auditors or monitors to assist in locating, reviewing and preparing files for inspection.

10.7 ARCHIVING STUDY RECORDS

At the close of the trial, investigators will be instructed in the requirements for records retention. Source documents, as well as the investigator's copies of the CRFs, must be retained for a minimum of two years after discontinuation of the IND. A date will be provided to the investigator by CSP. Do not destroy any records without CSP authorization.

In some cases, it may be necessary to retain study files longer, depending on local policy. Contact CSPCC if record storage becomes a problem at the site. CSPCC will authorized records disposal or discuss alternative storage locations.

11 Drug & Device Use Information

11.1 Simvastatin (Zocor®)

11.1.1 Laboratory Monitoring

- baseline AST and ALT
- repeat AST and ALT semiannually for the first year of treatment or until one year after the last elevation in dose. Patients titrated to the 80 mg dose should receive an additional test at 3 months. If a subject has > 3 times the upper limit of normal (ULN), a second liver function evaluation to confirm the finding should be performed. Should an increase in AST or ALT > 3 X ULN persist, the dose of simvastatin should be reduced or simvastatin should be discontinued.

Anticipated LDL and TG Response to Simvastatin

Dose (mg)	% LDL reduction	% TG reduction
10	- 33	- 10
20	- 33	- 19
40	- 40	- 19
80	- 48	- 23

11.1.2 Myopathy and Rhabdomyolysis

Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (CK) [>10 X ULN]. Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely. Patients starting therapy with simvastatin should be advised to report promptly unexplained muscle pain, tenderness or weakness. If myopathy is suspected, a CK level should be performed. A CK level above 10 X ULN in a patient with unexplained muscle symptoms indicates myopathy and simvastatin should be discontinued in this case. If the CK level is within normal limits, simvastatin may be continued. If the CK level is >5 X ULN, the simvastatin dose may be reduced and careful monitoring of the patient symptoms and CK levels should continue.

Simvastatin should be temporarily withheld in any subject with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of acute renal failure from rhabdomyolysis, such as severe acute infection, hypotension, major surgery, trauma, severe metabolic disorders, and uncontrolled seizures.

11.1.3 Contraindications for Prescribing Simvastatin in COURAGE

- known hypersensitivity to simvastatin or to other marketed statins
- active liver disease or unexplained persistent elevations of serum transaminases
- administration of gemfibrozil, fenofibrate, cyclosporine, and nefazodone. If a course of macrolide antibiotics (erythromycin, azithromycin, or clarithromycin) or systemic azole antifungals are prescribed during the course of the study, simvastatin therapy should be temporarily interrupted.

11.1.4 Equivalency

Simvastatin Equivalency Table

Other Statin Dose @ Baseline	Substitute with this Dose of Simvastatin
A 40-80	S 80
A 20	S 40
A 10	S 20
L 80	S 40
L 40	S 20
L 20	S 10
P 40	S 20
P 20	S 10
F 80	S 20
F 40	S 10
F 20	S 10
C 0.3	S 10
C 0.2	S 10

Abbreviation	Generic	Trade	Doses (mg)
A	atorvastatin	Lipitor	10, 20, 40, 80
C	cerivastatin	Baycol	0.2, 0.3
F	fluvastatin	Lescol	20, 40
L	lovastatin	Mevacor	10, 20, 40
P	pravastatin	Pravachol	10, 20, 40
S	simvastatin	Zocor	5, 10, 20, 40

Other Lipid Drugs

Statins: see list above
Resins: cholestyramine (Questran, Questran Lite, Prevalite); colestipol (Colestid)
Fibrates: gemfibrozil (Lopid); fenofibrate (Tricor)
Niacin: many immediate and slow release preparations

11.2 Slow release Niacin (NIASPAN®)

11.2.1 Indication in COURAGE:

LDL < 85 mg/dl (2.21 mmol/L) in subjects on 10 mg of simvastatin and TG > 200 mg/dl (2.26 mmol/L) or HDL < 35 mg/dl (0.91 mmol/L).

11.2.2 Contraindications:

- subjects with known hypersensitivity to niacin
- significant or unexplained hepatic dysfunction
- active peptic ulcer disease
- arterial bleeding

Relative Contraindications:

- diabetes, poorly controlled (HbA1c > 9%)
- active gout, hyperuricemia

Warnings:

- Niaspan should not be substituted for equivalent doses of immediate-release niacin. For patients switching from immediate-release niacin to Niaspan, therapy should be started in the same fashion as for patients starting Niaspan who have not been taking immediate-release niacin.
- Niaspan should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.
- In patients taking concomitant simvastatin, the dose of simvastatin should generally not exceed 10 mg.

11.2.3 Anticipated LDL and TG Response to Niaspan

Dose (mg)	% LDL reduction	% HDL increase	% TG reduction
1000	-9	+15	-11
1500	-14	+22	-28
2000	-17	+26	-35

11.2.4 Laboratory Monitoring:

AST, ALT, fasting glucose, uric acid, and CK at:

- baseline (before starting Niaspan)
- after 4-6 weeks of 1,000 mg qhs
- after 4-6 weeks of 1,500 mg qhs
- after 4-6 weeks of 2,000 mg qhs
- every 6 months on a stable dose of Niaspan

11.2.5 PRESCRIBING NIACIN

Niaspan

Niaspan should be taken at bedtime, after a low-fat snack. Therapy must be initiated with a starter pack, which covers the first 3 weeks. The dosing is as follows:

Week #	Niaspan Tablet Used	# Tablets	Nightly Dose
1	375 mg	1 tablet qhs	375 mg
2	500 mg	1 tablet qhs	500 mg
3	750 mg	1 tablet qhs	750 mg
4-7	500 mg	2 tablets qhs	1000 mg
*	750 mg	2 tablets qhs	1500 mg
*	1000 mg	2 tablets qhs	2000 mg

*After week 7, titrate to patient response and tolerance. Cannot titrate above 1,000 mg without checking labs. Daily dose of Niaspan should not exceed 2000 mg. In some instances, switching to immediate-release niacin and titrating the daily dose above 2000 mg may be appropriate.

If flushing is bothersome, 325 mg aspirin (not enteric coated) should be recommended 30 minutes prior to taking Niaspan.

Immediate Release (IR) Niacin

Canadian sites may not have access to Niaspan, at least during the initial phase of the trial, in which case immediate release niacin may be used. Below is a recommended guideline for prescribing IR niacin. BID dosing rather than TID dosing is recommended to enhance compliance, but some investigators may prefer to prescribe IR niacin TID.

Week #	Tablet Used	# Tablets (dose)	Total Daily Dose
1	100 mg	1 tablet (100 mg) bid with meals	200 mg
2	1/2 of 500 mg	1/2 tablet (250 mg) bid with meals	500 mg
3	500 mg	1 tablet (500 mg) bid with meals	1000 mg
4-7	$1^{1/2}$ 500 mg	$1^{1/2}$ tablets bid with meals	1500 mg

Laboratory Monitoring:
AST, ALT, fasting glucose, uric acid, and CK at:

- baseline (before starting IR niacin)
- after 4-6 weeks of 1,500 mg/day

If a higher dose of IR niacin is required to achieve secondary goals, please contact COURAGE lipid consultant.

11.3 TIROFIBAN

(Aggrastat®)

11.3.1 INDICATIONS AND USAGE

Tirofiban in combination with heparin, is indicated for the treatment of acute coronary syndrome, including patients who are to be managed medically and those undergoing PTCA or atherectomy. In this setting, tirofiban has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure.

11.3.2 CONTRAINDICATIONS TO TIROFIBAN

1. Known hypersensitivity to any component of the product.
2. Active internal bleeding or history of bleeding diathesis within the previous 30 days
3. History of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm
4. History of thrombocytopenia following prior exposure to tirofiban
5. History of stroke within 30 days or any history of hemorrhagic stroke
6. Major surgical procedure or severe physical trauma within the previous month
7. History, symptoms, or findings suggestive of aortic dissection
8. Severe hypertension (systolic blood pressure > 180mmHg and/or diastolic blood pressure >110 mmHg).
9. Concomitant use of another parenteral GP IIb/IIIa inhibitor
1. Acute pericarditis

11.3.3 RECOMMENDED DOSAGE OF TIROFIBAN

In clinical trials establishing efficacy and in currently recommended use, tirofiban is given to patients with unstable angina or non-Q wave myocardial infarction as a two-staged intravenous infusion regimen of a loading infusion of 0.4 μg/kg/min for 30 minutes followed by a maintenance infusion of 0.1 μg/kg/min. This dose produces approximately 90% inhibition of the ex-vivo ADP-induced platelet aggregation with a 2.9 fold prolongation of bleeding time during the loading infusion. Inhibition persists over the duration of the maintenance infusion.

U.S. Investigators: For further information please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the product circular included in the Pharmacy Handbook.

Canadian Investigators: Aggrastat is not a marketed product in Canada. For further information please refer to the Confidential Investigators Brochure provided by MERCK Frosst.

11.4 Lisinopril

(Prinivil®)
For specific information about dosing, indications, and contraindications

US Sites please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Product Circular included in the Pharmacy Handbook

Canadian sites please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the International Product Circular located in the Pharmacy Handbook.

11.5 Losartan

(Cozaar®)
For specific information about dosing, indications, and contraindications

US Sites please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Product Circular included in the Pharmacy Handbook

Canadian sites please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Worldwide Product Circular, also located in the Pharmacy Handbook.

11.6 Losartan and Hydroclorathiazide

(Hyzaar®)
For specific information about dosing, indications, and contraindications

US Sites please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Product Circular included in the Pharmacy Handbook

Canadian sites please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Worldwide Product Circular, also located in the Pharmacy Handbook.

11.7 Isosorbide 5-mononitrate

(Imdur®)

For specific information about dosing, indications, and contraindications

please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Product Circular included in the Pharmacy Handbook

11.8 Amlodipine

(Norvasc®)

For specific information about dosing, indications and contraindications please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Product Circular included in the Pharmacy Handbook.

11.9 Metoprolol XL

(Toprol XL®)

US sites. For specific information about dosing, indications, and contraindications please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Product Circular included in the Pharmacy Handbook

Canadian Sites. Metoprolol XL is not a marketed product in Canada. It will, however, be included in the IND submitted to the Health Protection Board and, on approval, distributed by the PCC. Canadian sites please refer to the information in the Pharmacy Handbook for dosing, indications, and contraindications.

11.10 Tc99m Sestamibi

(Cardiolite®)

Tc-99m sestamibi should be used in the following dose.

Patient Weight (lbs.)	*Dose of Tc-99m Sestamibi (mCi)*
< 185	*25*
185-225	*30*
> 225	*35*

Please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Product Circular included in the Pharmacy Handbook for warnings and contraindications.

11.11 Adenosine

(Adenoscan®)

US Sites. Please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the Product Circular included in the Pharmacy Handbook.

Canadian Sites.
Adenosine is available for compassionate use in Canada.

11.12 Contrast Material

(Visipaque®)

Please see package insert available in your pharmacy or radiology department for indications and contraindications.

CHD patients with diabetes who undergo cardiac catheterization should receive non-ionic contrast media to minimize the risk of subsequent renal failure.

11.13 Vasoseal Devices

(Vasoseal VHD®, Vasoseal ES®)

Datascope representatives will contact all sites and train site personnel in the use of the devices. For instructions, indications and contraindications please see the product information booklets in the Pharmacy Handbook Section.

12 Administrative, Budget, and Travel Information

12.1 Which Chairman's Office to Contact

For practical reasons each site has been assigned to a Study Co-chairman to approach first with study related questions, in particular for medical questions. If this first contact fails, the other Study Cochairman can always be approached. It is not an exclusive assignment. The assignments are

A) All Canadian sites first contact Dr Boden's office

B) All US non-VA sites first contact Dr O'Rourke's office

C) The VAs are split

Ann Arbor, Durham, Iowa, New York, San Antonio, Seattle contact Dr Boden's Office

Albuquerque, Atlanta, Houston, Lexington, Little Rock, Nashville contact Dr O'Rourke's office.

Forms should be sent to the assigned Study Cochairman's office.

12.2 FEDEX Account

A Fedex account has been set up for this study. This account should be used to send specimens or films to the core laboratories.

The account number is 235-317-516.

12.3 Other Contact Information

12.4 Computers

If the computer fails to boot up, a “new” boot should be attempted using the backup boot disk that has been provided to you. If this fails call the coordinating center for further instructions.

If the computer is broken or stolen also call the Coordinating Center.

If the Epimetrics application fails to load and the instructions in Section 9 don’t seem to work, call the economic core laboratory for further help.

If there are any other hardware or software problems please alert the Coordinating Center as soon as is reasonable.

12.5 BUDGETARY PROCEDURES

12.5.1 . Budget Issues (VA Centers)

1. Funding Support FY1999 (January 1999-September 1999) - All centers will be provided with personnel funds for 1 full-time study coordinator and a half-time program assistant. The study coordinator will be maintained at full time throughout the study. The program assistant will be maintained at half-time through the patient intake period (36 months) and six months of the follow-up period for a duration of 3.5 years. All other funds in the amount of $2,900 will be sent to each participating center this fiscal year. The all other funds are to be used for the purchasing of miscellaneous office & medical supplies, mailings, copy charges, and pager rental. Once the budget request is received at the West Haven CSP Coordinating Center, it is reviewed and forwarded to the Cooperative Studies Program in VA Headquarters to be allocated to your center. The FY1999 will end September 30, 1999. All funds received at your station should be spent by the end of this time or reported for withdrawal. Each VA has a different cut off date for ordering, please check with your research office and submit your orders prior to this date.

2. Equipment - An additional $700 will be sent in the all other funds to purchase a fax and answering machine dedicated for the study. All computer equipment required for this study has been purchased and will be distributed to each center. The equipment is as follows:

(1) Fujitsu Pentablet (Point 510) (Value $2,740)
(Includes software, backpack & stand)

(2) HP Deskjet 695C (Value $174)

3. Future Year Budgets - Budget requests are made a year ahead. A form "Request for Budgetary Support" (Attachment A) has been sent with an accompanying letter to all VA participating centers ACOS/R&D offices for Fiscal Year (FY) 2000 (October 1999 - September 2000). Actual personnel costs should be listed on this form and all other funds. If there are circumstances, and additional funding is required, a justification will need to be included on the form. This form is signed by the Participating Investigator and the ACOS for R&D and then mailed back to the West Haven-CSPCC. The figures will be reviewed and consolidated, questions will be referred back to the Research Office. This request will be coordinated with your Research Office. Personnel funding for each participating medical center will end one month after the patient follow-up period except for the program assistant position that ends 7 months after the patient intake period (6 months follow-up plus one month for closeout).

4. Funding Sources - The Cooperative Studies Program will provide personnel and all other funds to each participating center in support of this study. The funds may be sent as Program 870/Medical Care (nurses), Program 825/Medical Research (personnel other than nurses and all other funds) or non-VA funds sent to the local VA general post fund or non-profit organization.

12.5.2 BUDGETARY ISSUES (NON VA SITES)

These sites will be funded using a capitation model. We will begin with a letter of agreement, but eventually a contract will be signed. Sites will be provided with an initial payment of $5,000 and then reimbursed quarterly based on dataforms received at the coordinating center.

The computer equipment required for this study has been purchased and will be distributed to each center. The equipment is as follows:

(1) Fujitsu Pentablet (Point 510) (Value $2,740)
(Includes software, backpack & stand)

(2) HP Deskjet 695C (Value $174)

12.6 General Procedures

1. Requesting Additional Funding - Any requests for additional funding must be approved by the Study Chairman and the West Haven-CSPCC. Please submit your request with justification to the Director, WH-CSPCC, through Dr. William Boden, Study Co-Chairman (addresses below). The request will be reviewed and a written response will be made. These requests must be coordinated and sent from your Research Office. Requests can be faxed to the appropriate offices.

Peter Peduzzi, Ph.D.
Director
CSPCC/151A
VA Connecticut Healthcare
950 Campbell Avenue
West Haven, CT 06516

FAX: (203) 937-3858

William Boden, M.D.
Study Co-Chairman (CSP#424)
Director of Cardiology
Hartford Hospital
80 Seymour Street
Hartford, CT 06102

FAX:

Robert O'Rourke, MD
Study Co-Chairman (CSP 424)
Chief, Cardiology
Audie Murphy VA Medical Center
7400 Merton Minter Blvd.
San Antonio, TX 78284

FAX: 210 567-4687

2. Change of Principal Investigator - Adequate notice to WH-CSPCC must be given if there's going to be a change of PI. This will ensure continuity of funds. A letter from the PI should be sent to Dr. Boden informing him of this change with a termination date and recommendation of a new PI. A CV for the new PI should be included with the letter of recommendation. Dr. Boden will submit a letter with his concurrence to the WH-CSPCC. This change of investigator will also have to be submitted and approved by your local R&D Committee. The WH-CSPCC and the Albuquerque Pharmacy must have copies of the R&D minutes from the medical center approving this change. The WH-CSPCC will issue a letter to the R&D office requesting the minutes upon notification of a PI change.

   If an Investigator's VA status changes during the study to less than 5/8, WH-CSPCC must be notified. In order to receive funding an Investigator should be 5/8 VA or receive approval through the VA Headquarter's Eligibility Panel. Your Research Office is familiar with this procedure and can submit the required paperwork for you. WH-CSPCC must have a copy of the VA Headquarter's approval.

3. Center Correspondence Form - When a change in the PI or local study coordinators is going to be made, a form for the current PI or study coordinator should also be faxed as soon as possible to the West Haven-CSPCC.

4. VA Centrally Directed Travel - Upon receiving a request from the Study Co-Chairmen or Biostatistician to hold a study meeting, the West Haven CSPCC will prepare an estimate of the travel costs to the study meeting. This information will be forwarded to VA Headquarters. A TWX (see Attachment B) authorizing your travel from VA Headquarters will be advanced to your station so that you may initiate your travel arrangements and orders. The TWX sent will designate whether the travel funds will be sent as VA or non-VA dollars. Funding will be provided to your center either prior to travel or after. You must always notify your R&D office when you will be traveling and coordinate your travel with that office.

I am available for any assistance or information that you may require at the West Haven Cooperative Studies Program Coordinating Center.

Peggy Antonelli, Administrative Officer, West Haven-CSPCC, Phone: (203) 932-5711 ext. 3782; FAX (203) 937-3848

12.7 Supply requests

The supply request form is located on the next page. Photocopy for your use. This form can be FAXED to West Haven CSPCC when supplies are needed.

Fax #'s: 203-937-3858 or 888-803-7439

Contact ECOR for teleform master copies of the Economic and Quality of Life CRF's:

Form 20B	Patient Economic Questionnaire (PEC) Baseline
Form 20F	Patient Economic Questionnaire (PEC) Follow-up
Form 21	Social Support Index
Form 22	Seattle Angina Questionnaire (SAQ)
Form 23	Symptom Distress Scale
Form 24	SF 36 – Health Status Survey
Form 25	Mood Screen
Form 27	Self-Management Difficulties Scale

Note: Form 26 Standard Gamble/Trader – there is no paper version of this form

REQUEST FOR SUPPLIES VA CSP #424: COURAGE TRIAL	
TO: WH-CSPCC Hospital #: _____ **FROM:**	**Date of request** **_____/_____/_____**
Item Requested	**Quantity**
Form 01 Screening/Eligibility Log	
Form 02 Randomization	
Form 2A Angiography Worksheet	
Form 03 Patient Information	
Form 04 Baseline History & Status	
Form 05 ECG Labels	
Form 06 Exercise/Stress Test	
Form 07 Imaging Evidence of Ischemia	
Form 08 Laboratory Values	
Form 09 Cardiovascular Medications	
Form 10 PCI Procedure	
Form 11 Hospitalization	
Form 11A Suspected MI Event	
Form 12 Cardio/Cerebro Vascular Tests	
Form 13 Follow-Up Visit & Outpatient Procedures	
Form 14 PACE Worksheets	
Form 15 MEDFICTS	
Form 16 Missed Visit Notification	
Form 17 Non-Routine Term. from Study Protocol	
Form 19 Report of Death	
Mailing Labels	
Co-Chairman's Office: San Antonio___ Syracuse ___	
West Haven CSPCC	

Please note: Please allow sufficient time for shipment.
FAX requests to WH-CSPCC
Fax #'s: 203-937-3858 or 888-803-7439

REQUEST FOR SUPPLIES VA CSP #424: COURAGE TRIAL	
TO: WH-CSPCC Hospital #: _____ **FROM:**	**Date of request** **_____/_____/_____**
PACE Worksheets	**Quantity**
PACE Physical Activity:	
Getting Out of Your Chair	
Planning the First Step	
Keeping the PACE	
PACE Nutrition:	
Good Health: It's A Matter of Choice	
Charting a Course for Change	
Healthful Eating for the Long Run	
Focus on Fiber, Fruits & Vegetables	
The Balancing Act	
Trimming the Fat	
PACE Smoking:	
Putting Tobacco in Its Place	
Thinking About Quitting Smoking	
Smoke Free for Good	
Checklists	
Pre Randomization/Randomization	
Baseline	
Scheduled Follow-up Visits	
Intercurrent Hospitalization	
Early Termination	

Please note: Please allow sufficient time for shipment.
FAX requests to WH-CSPCC
Fax #'s: 203-937-3858 or 888-803-7439

12.8 WEST HAVEN CENTER CORRESPONDENCE FORM

The Center Correspondence Form is located on the next page. Whenever there are changes in mailing address, telephone numbers, or change in participating investigator or nurse coordinator, complete the form with changes and FAX to WH-CSPCC as soon as possible. Photocopy the following page for your use.

Refer to the Operations Manual at your site for the following form:

12.8.1 Change of Investigator

12.8.2 Change of Coordinator

12.9 Request for Supplies from the Economic Center

Disks
Disk mailers

Original versions of the QOL forms i.e. not photocopied

In particular the PEC since it is not on the pentablet